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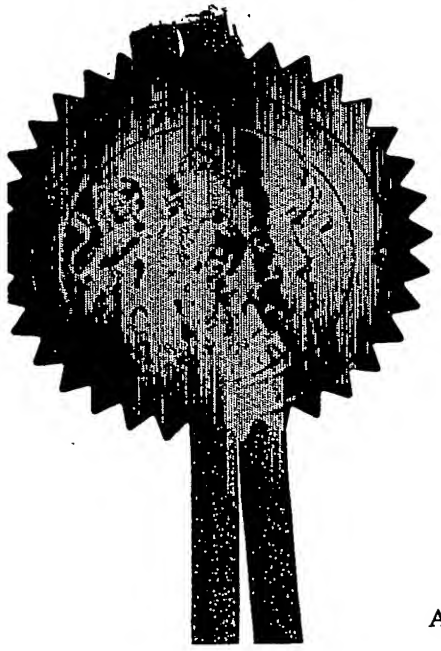

Signed P. Mahoney

Dated 15 December 2003

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1. Your reference — P-15172

2. Patent application number *(The Patent Office will fill in this part)* — 0219690.5 — 23 JUL 2002

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

ELI LILLY AND COMPANY,
LILLY CORPORATE CENTER,
INDIANAPOLIS,
INDIANA 46285, USA

0042 89 04002

Patents ADP number *(if you know it)* — 428904002

If the applicant is a corporate body, give the country/state of its incorporation — STATE OF INDIANA, U.S.A.

4. Title of the invention — BENZYL MORPHOLINE DERIVATIVES

5. Name of your agent *(if you have one)* — VAUGHAN, Jennifer Ann

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

LILLY RESEARCH CENTRE,
ERL WOOD MANOR,
WINDLESHAM,
SURREY, GU20 6PH, UK

08451042001

Patents ADP number *(if you know it)*

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Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

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a) any applicant named in part 3 is not an inventor, or
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Patents Form 1/77

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Description	55
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Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	1
Request for substantive examination *(Patents Form 10/77)*	
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11. I/We request the grant of a patent on the basis of this application.

Signature [signature] Date 23 August 2002

12. Name and daytime telephone number of person to contact in the United Kingdom — Georgina L Howard 01276 483443

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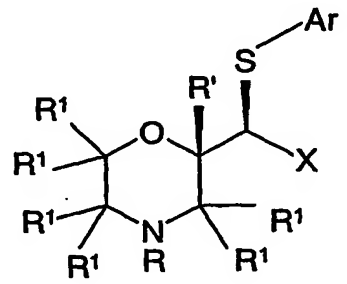
BENZYL MORPHOLINE DERIVATIVES

This invention relates to novel benzyl morpholine compounds, and to their use in selectively inhibiting norepinephrine reuptake.

Selective inhibition of norepinephrine reuptake is a relatively new mode of action for the treatment of affective disorders. Norepinephrine appears to play an important role in the disturbances of vegetative function associated with affective, anxiety and cognitive disorders. Tomoxetine hydrochloride is a selective inhibitor of norepinephrine, and is currently under development for the treatment of attention deficit hyperactivity disorder (ADHD). Reboxetine is a marketed selective norepinephrine reuptake inhibitor for the treatment of depression.

According to the present invention there is provided a compound of formula (I)



wherein:

R is H;

Ar is a phenyl group;

X is a phenyl group;

R' is H or C_1-C_4 alkyl;

each R^1 is independently H or C_1-C_4 alkyl; and pharmaceutically acceptable salts thereof.

The group Ar may be substituted or unsubstituted phenyl. For example, Ar may be unsubstituted phenyl or, preferably phenyl substituted with 1, 2, 3, 4 or 5 substituents, preferably with 1 or 2, for example 1, substituent. The substituted phenyl group is preferably substituted in the 2- position. Suitable substituents include C_1-C_4 alkyl, O(C_1-C_4 alkyl), S(C_1-C_4 alkyl), halo, and phenyl optionally substituted with, for example, halo, C_1-C_4 alkyl, or O(C_1-C_4 alkyl).

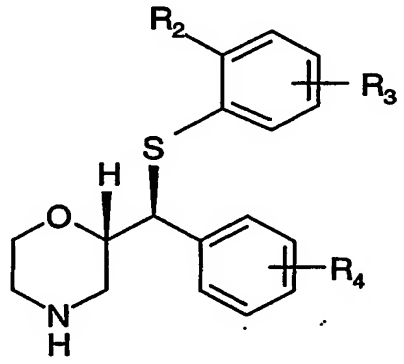
The group X may be substituted or unsubstituted phenyl. For example, X may be phenyl substituted with 1, 2, 3, 4 or 5 substituents, preferably with 1 substituent. Suitable substituents include C_1-C_4 alkyl, O(C_1-C_4 alkyl), and halo.

"C_1-C_4 alkyl" as used herein includes straight and branched chain alkyl groups of 1, 2, 3 or 4 carbon atoms, and may be unsubstituted or substituted. C_1-C_2 alkyl groups are preferred. Suitable substituents include halo. Thus the term "C_1-C_4 alkyl" includes haloalkyl.

"Halo" includes F, Cl, Br and I, and is preferably F or Cl.

A particularly preferred substituted C_1-C_4 alkyl group for the group Ar is trifluoromethyl.

A preferred group of compounds according to the present invention is represented by the formula (II);



(II)

wherein

R_2 and R_3 are each independently selected from H, C_1-C_4 alkyl, O(C_1-C_4 alkyl), S(C_1-C_4 alkyl), halo and phenyl; and

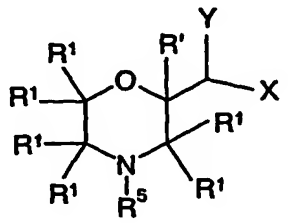
R_4 is selected from H and C_1-C_4 alkyl; and pharmaceutically acceptable salts thereof.

R_2 is preferably C_1-C_3 alkyl, O(C_1-C_3 alkyl), F or Ph. R_3 is preferably H. R_4 is preferably H.

Compounds of the present invention are selective inhibitors of norepinephrine reuptake. Advantageously, they have a reduced interaction with the liver enzyme CYP2D6 compared with other norepinephrine-reuptake inhibitors,

such as reboxetine. They are indicated for the treatment of disorders associated with norepinephrine dysfunction in mammals.

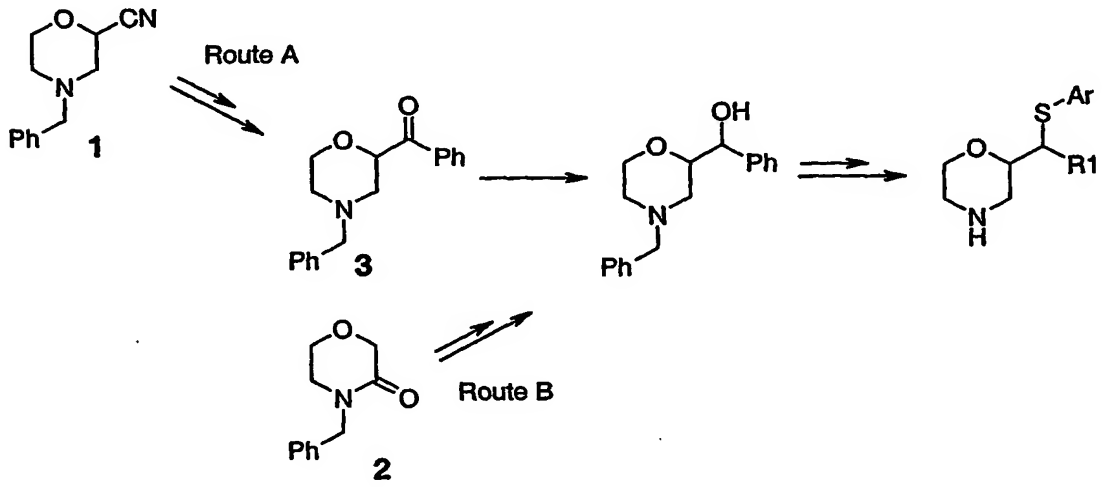
Compounds of the present invention may be prepared by reacting a compound of the formula II:



II

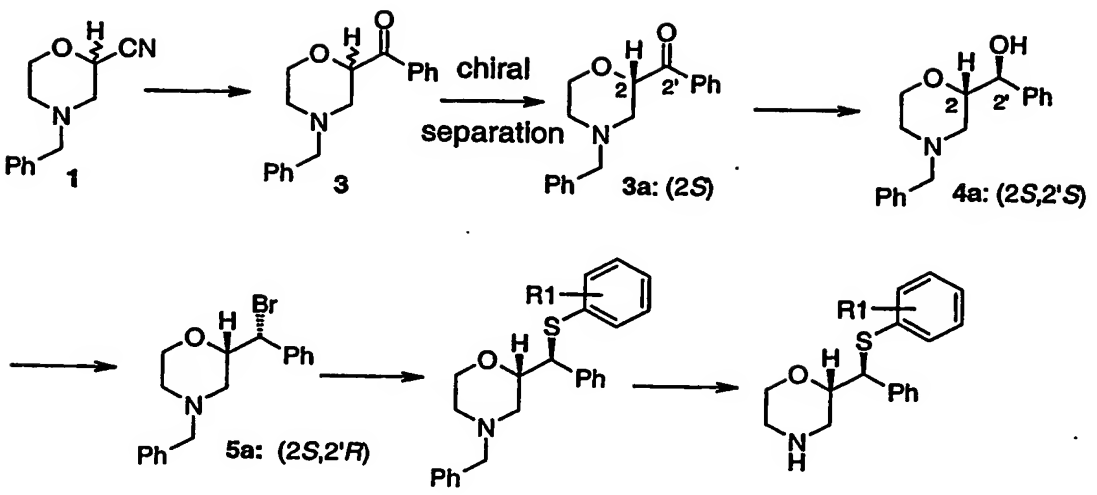
where R5 is a protecting group, e.g. benzyl, and X, R' and R^1 are as formula I above and Y is a leaving group, with an aryl thiol. Examples of suitable leaving groups include halo and mesylate, but the nature of the leaving group is not critical.

For example, compounds of the present invention may be prepared by conventional organic chemistry techniques from N-benzyl-cyanomorpholine 1 (Route A) or N-benzyl-morpholinone 2 (Route B) as outlined in Scheme 1 below:



Scheme 1

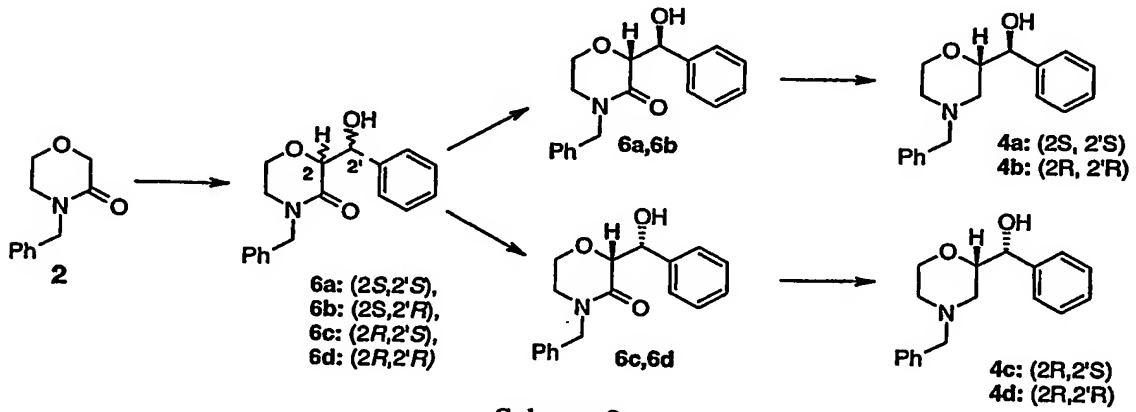
More detail of Route A is given in Scheme 2:



Scheme 2

The amino alcohol 3a can be obtained by reaction of N-benzyl-cyanomorpholine 1 with a Grignard reagent, followed by acid hydrolysis to give racemic phenyl ketone 3 which may be separated on chiral HPLC. (2S)-Phenyl ketone 3a may then be reduced with DIP-Cl to give 4a in high diastereomeric excess. The amino alcohol 4a is converted into benzyl bromide 5a, to give the desired N-substituted aryl thio morpholines after displacement with the requisite aryl thiol. Deprotection of the tertiary amine gives the final products.

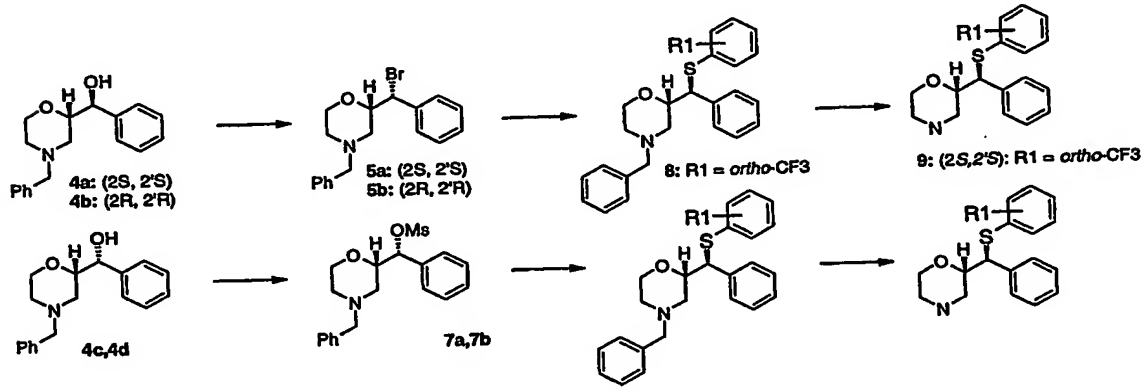
Detail of route B is given in Scheme 3:



Scheme 3

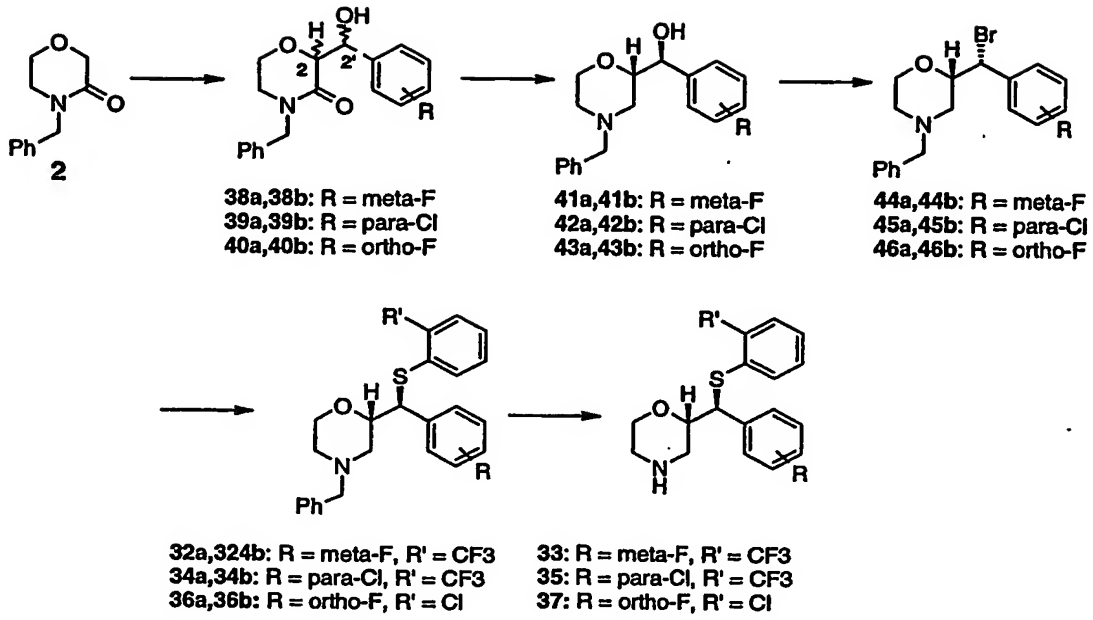
Treatment of *N*-benzyl morpholinone 2 with a strong base such as lithium diisopropylamide at low temperature followed by addition of benzaldehyde gives aldol adducts 6a-6d as a 2:1 mixture of diastereomer pairs 6a,6b and 6c,6d, which may be separated using conventional chromatographic techniques. Reduction with a borane reagent at elevated temperatures gives diasteremeric amino alcohol pairs 4a,4b and 4c,4d respectively.

Amino alcohol pair 4a,4b may be converted to bromide 5a,5b and further to racemic aryl thio morpholines as outlined in Scheme 4. Amino alcohol pair 4c,4d may be converted into the corresponding mesylate. Displacement with the requisite thiol, followed by removal of the nitrogen protecting group furnishes aryl thiol morpholines as racemic mixtures of two diastereomers. The racemic aryl thiol morpholines may be separated into enantiomerically pure products using chiral HPLC technology.



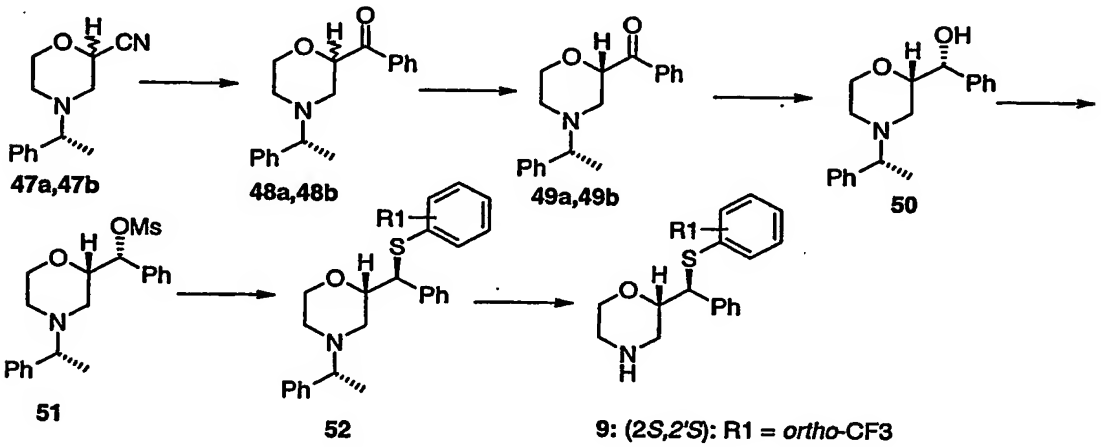
Scheme 4

Aryl-substituted morpholines 33, 35, 37 may be obtained from morpholinone 2 as outlined in Scheme 5:



Scheme 5

An alternative route to 9 is outlined in Scheme 6. This route makes use of a chiral auxiliary and gives 9 in enantiomerically pure form.



Scheme 6

In addition to the compounds of formula I and formula II, and processes for the preparation of said compounds, the present invention further provides pharmaceutical compositions comprising a compound of formula I or formula II or

a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable diluent or carrier.

Further, the present invention provides a compound of formula I or formula II or a pharmaceutically acceptable salt thereof, for use as a pharmaceutical; and a compound of formula I or formula II or a pharmaceutically acceptable salt thereof, for use as a selective inhibitor of the reuptake of norepinephrine.

The present compounds and salts may be indicated in the treatment of disorders associated with norepinephrine dysfunction in mammals, including affective, anxiety, and cognitive disorders.

Disorders associated with norepinephrine dysfunction in mammals include, for example, nervous system conditions selected from the group consisting of an addictive disorder and withdrawal syndrome, an adjustment disorder, an age-associated learning and mental disorder, anorexia nervosa, apathy, an attention-deficit disorder (ADD) due to general medical conditions, attention-deficit hyperactivity disorder (ADHD), bipolar disorder, bulimia nervosa, chronic fatigue syndrome, chronic or acute stress, conduct disorder, cyclothymic disorder, depression, dysthymic disorder, fibromyalgia and other somatoform disorders, generalized anxiety disorder, incontinence, an inhalation disorder, an intoxication disorder, mania, migraine headaches, obesity, obsessive compulsive disorders and related spectrum disorders, oppositional defiant disorder, panic disorder, peripheral neuropathy, post-traumatic stress disorder, premenstrual dysphoric disorder, a psychotic disorder, seasonal affective disorder, a sleep disorder, social phobia, a specific developmental disorder, selective serotonin reuptake inhibition (SSRI) "poop out" syndrome, TIC disorders, cognitive disorders including mild cognitive impairment (MCI), dementia of the Alzheimers type (DAT), vascular dementia and cognitive impairment associated with schizophrenia (CIAS), hypotensive states including orthostatic hypotension, and pain including chronic pain, neuropathic pain and antinociceptive pain. The compounds of the present invention are particularly suitable for the treatment of attention deficit hyperactivity disorder, ADHD.

Thus, the present invention also provides a compound of formula I or formula II for selectively inhibiting the reuptake of norepinephrine; and a compound of formula I or formula II for treating disorders associated with norepinephrine

dysfunction in mammals; and the use of a compound of formula I or formula II, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for selectively inhibiting the reuptake of norepinephrine; and the use of a compound of formula I or formula II, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of disorders associated with norepinephrine dysfunction in mammals, including the disorders listed herein.

Further, the present invention provides a method for selectively inhibiting the reuptake of norepinephrine in mammals, comprising administering to a patient in need thereof an effective amount of a compound of formula I or formula II or a pharmaceutically acceptable salt thereof; and a method for treating disorders associated with norepinephrine dysfunction in mammals, comprising administering to a patient in need thereof an effective amount of a compound of formula I or formula II or a pharmaceutically acceptable salt thereof.

The present invention includes the pharmaceutically acceptable salts of the compounds of formula I and formula II. Suitable salts include acid addition salts, including salts formed with inorganic acids, for example hydrochloric, hydrobromic, nitric, sulphuric or phosphoric acids, or with organic acids, such as organic carboxylic or organic sulphonic acids, for example, acetoxybenzoic, citric, glycolic, *o*- mandelic-l, mandelic-dl, mandelic d, maleic, mesotartaric monohydrate, hydroxymaleic, fumaric, lactobionic, malic, methanesulphonic, napsylic, naphtalenedisulfonic, naphtoic, oxalic, palmitic, phenylacetic, propionic, pyridyl hydroxy pyruvic, salicylic, stearic, succinic, sulphanilic, tartaric, 2-hydroxyethane sulphonic, toluene-p-sulphonic, and xinafoic acids.

In addition to the pharmaceutically acceptable salts, other salts are included in the invention. They may serve as intermediates in the purification of compounds or in the preparation of other, for example pharmaceutically acceptable, acid addition salts, or are useful for identification, characterisation or purification.

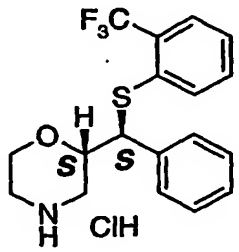
It will be appreciated that compounds of formula I and formula II possess asymmetric carbon atoms, and that the present invention is directed specifically to individual stereoisomers. The particular stereochemistry of the present compounds is essential to the pharmacological profile of the compounds.

The following examples illustrate compounds of the present invention and methods for their preparation .

Examples

Stereochemical conventions

The absolute stereochemistry of the following compound according to the present invention was determined as (2*S*,2'*S*) using X-ray crystallography.



X-ray crystallographic data for the above compound is listed in Tables 1-6 herein.

All of the Examples herein were obtained as single isomers either through the use of chirally pure starting material or chiral separation methods, such as HPLC.

General Synthetic Procedures for the preparation of Examples 1-15

The numbers included in the following Sections refer to the compounds illustrated on pages 4-6 herein.

General Procedure 1: Preparation of racemic N-*substituted aryl thiols*

To a solution of **5a,5b** (0.02 g, 0.52 mmol) and the requisite aryl thiol (1.1 eq) in anhydrous dimethylformamide (1 ml) at room temperature under nitrogen was added cesium carbonate (1.1 eq, 0.19 g, 0.57 mmol). The reaction mixture was heated to 95°C for 2 hours. The reaction mixture was allowed to cool to room

temperature, diluted with ethyl acetate, then washed sequentially with water, brine, dried over magnesium sulphate and finally concentrated *in vacuo*.

General Procedure 2: Deprotection of N-*substituted aryl thiols*

To a solution of the requisite *N*-benzyl aryl thiol in anhydrous dichloromethane (5ml) was added solid supported Hünig's base (Argonaut, 3.56 mmol/g, 2 eq) and α-chloroethyl chloroformate (3 to 10 eq) at room temperature under nitrogen. The reaction mixture was heated to 40°C and followed by LCMS analysis. After completion the reaction mixture was filtered, and the resin washed with dichloromethane. The combined organic phases were concentrated *in vacuo*. Methanol (HPLC grade, 25 ml) was added and the solution heated to 60°C for 1.5 to 4 hours. After complete consumption of starting material the methanol solution was evaporated to give a solid which was further purified as detailed for individual compounds.

General Procedure 3: Conversion of amines into hydrochloride salts

To a solution of the requisite amine in dry diethyl ether (1 ml) was added hydrochloric acid (500 μl of a 1M solution in diethyl ether). A white precipitate immediately formed. The suspension was then sonicated for 5 minutes. Ether was blown off with a stream of nitrogen and the samples were dried under high vacuum for several hours to give the hydrochloride salts in near quantitative yield as white solids.

General Procedure 4: Aldoladdition with substituted benzaldehydes

Preparation of 38a,38b; 39a,39b; 40a,40b

N-Benzylmorpholinone (1.0 eq) and the requisite aldehyde (1.1 eq) were dissolved in anhydrous tetrahydrofuran (25 ml) under nitrogen and the reaction cooled to -78°C. Then, lithium diisopropylamide (1.1 eq of a 2M solution in heptane/tetrahydrofuran/ethylbenzene) was added over approximately 20 minutes, whilst maintaining the reaction temperature below -78°C. The resulting yellow

solution was stirred at -78°C for 1 hour and then allowed to warm to room temperature. The reaction was quenched with saturated ammonium chloride solution (25 ml) and extracted into ethyl acetate. The combined organic layers were dried with magnesium sulphate, filtered and concentrated *in vacuo*, to give a yellow oil which was purified by column chromatography on silica gel (eluent: ethyl acetate/hexane 70/100 [v/v]).

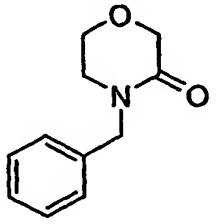
General Procedure 5: Reduction of substituted aldol adducts

Preparation of 41a,41b; 42a,42b; 43a,43b

To a solution of the requisite amide **38a,38b**, **39a,39b** or **40a,40b** (1.1 mmol) in anhydrous tetrahydrofuran under nitrogen at room temperature was slowly added borane in (4 eq of a 1M solution in tetrahydrofuran). The solution was stirred at 60°C for 2 hours. The reaction was cooled to room temperature; dry methanol (excess) was slowly added, followed by aqueous hydrochloric acid solution (1M, excess). The reaction mixture was heated to 60°C for 1 hour and quenched with aqueous potassium carbonate solution (1M, excess) and extracted with diethyl ether. The combined organic layers were washed with brine, dried with magnesium sulphate, filtered and concentrated *in vacuo* yielding a yellow oil which was purified by column chromatography on silica gel (eluent: ethyl acetate/hexane 10/100 [v/v]).

Preparation of intermediates for the synthesis of Examples 1-15

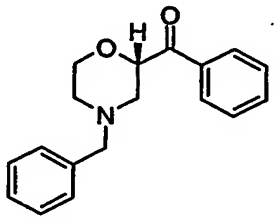
4-Benzylmorpholin-3-one (2)



A solution of *N*-benzyl-*N*-(2-hydroxyethyl) chloroacetamide (627.7 g, 2.76 mol) in *tert*-butanol (0.9 l) was stirred under nitrogen while warming to 25-30°C. Potassium tert-butoxide (2.897 l of a 1M solution in *tert*-butanol, 2.90 mol, 1.05 eq) was added over 2 hours. The reaction mixture was then stirred at room temperature for 90 minutes. Ice-cold water (6 l) was added and the resultant cloudy solution extracted with ethyl acetate. The combined organic layers were washed with brine,

dried over magnesium sulphate and evaporated *in vacuo* to give a light brown oil (441 g, 84%), which was used in the next stage without further purification; MW 191.23; $C_{11}H_{13}NO_2$; ^1H NMR ($CDCl_3$): 7.29-7.40 (5H, m), 4.67 (2H, s), 4.28 (2H, s), 3.87 (2H, t, 5 Hz), 3.31 (2H, t, 5 Hz); LCMS: (12 min method) m/z 192 [M+H]+ @ Rt 1.00 min.

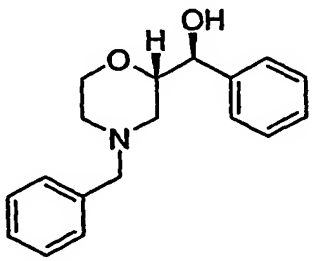
(2S)-(4-Benzyl-morpholin-2-yl)-phenyl-methanone (3a) and (2R)-(4-Benzyl-morpholin-2-yl)-phenyl-methanone (3b) preparation *via* Route A in Scheme 1



A 3l double jacket reactor was charged with **1** (135.05 g; 1eq) (King, F.K.; Hadley, M.S.; Joiner, K.T.; Martin, R.T.; Sanger, G.J.; Smith, D.M.; Smith, G.E.; Smith, P.; Turner, D.H.; Watts, E.A., J. Med. Chem. 1993, 36(6), 683.) and dry diethyl ether (1.4 l). When Tj=0°C and Tm=1°C phenyl magnesium chloride (2M sol. in tetrahydrofuran, 360 ml, 1.08 equiv) was added dropwise over 1hour. Tm rose to 4°C and came back to 2°C at the end of the addition. Tm was progressively raised to 17.5°C within 45 minutes and the mixture stirred at this temperature for another 45 minutes. The reactor was cooled down to Tm=2°C and Tj=0°C (75 minutes) and hydrochloric acid (700ml of 5N solution) was added in two portions. Tm rose to 33°C. After some minutes, the hydrochloride salt of the ketone crystallised. When Tm=Tj=room temperature, the triphasic suspension was filtrated. The organic layer of the mother liquors, which contains impurities, was eliminated. The filtration cake was then washed with methylene chloride (700 ml). This liquor was charged in the reactor with the acid aqueous layer. Treatment of the hydrochloride salt: After drying under vacuum, 164.4 g of the hydrochloride contaminated with $MgCl_2$ were suspended in a biphasic mixture of water/methylenchloride (500 ml/800 ml). The suspension was basified with aqueous sodium hydroxide (75 ml of a 30% solution) under ice bath cooling. $Mg(OH)_2$ precipitated and the aqueous layer was extracted with methylene chloride. The organic layers are filtrated on a bed of Celite 512 after

adding some Celite to the layers themselves. The filtrated organic phase was dried over magnesium sulphate and evaporated to dryness. The ketone crystallizes readily on standing (132.4 g; 70%). Treatment of the mother liquors: The combined organic phases were washed with aqueous sodium hydroxide (750ml of a 2N solution). Celite 512 (160 g) was added to the suspension which was then filtrated through a bed of Celite. The aqueous layer was separated and extracted with methylene chloride. The combined organic phases were dried over magnesium sulphate and evaporated to dryness to provide 35.8 g of **3a,3b** enriched with unreacted nitrile. Compound **3a** was obtained after separation using chiral HPLC on a Daicel chiralpak AD 20µm column with 100% Ethanol / 0.3% DMEA as eluent at a flow rate of 150ml/min and UV-detection at 300nm.

(*S*)-Phenyl[(2*S*)-4-(phenylmethyl)morpholin-2-yl]methanol (4a)

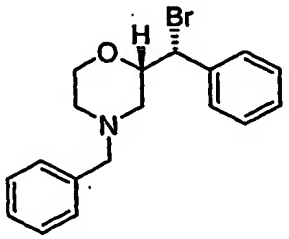


To a stirred solution of [(-)-*B*-chlorodisopinocampheylborane] (45 g, 140 mmol) in dry tetrahydrofuran (300 ml) under nitrogen was added **3a** (7.97 g, 28.4 mmol) in one portion. The reaction mixture was stirred at room temperature for 18 hours. The mixture was evaporated *in vacuo* and extracted from 2M aqueous sodium hydroxide solution into ethyl acetate. The combined organic extracts were washed with brine, dried, filtered and evaporated. The crude product was taken up in chloroform/methanol (1:1 [v/v]) and absorbed onto 150g SCX-2 ion exchange resin. After elution of borane residues with methanol the product was eluted with 2M ammonia in methanol. Removal of solvent *in vacuo* yielded the product as yellow oil. This was further purified by flash chromatography (eluent: ethyl acetate/isohexane 80/20 [v/v]). After removal of solvents, the product crystallised on standing (6.73g, 84%); MW 283.37; $C_{18}H_{21}NO_2$; ^1H NMR ($CDCl_3$): 7.32-7.45

(10H, m), 4.67 (1H, d, 7 Hz), 4.03 (1H, dt, 11 Hz and 2 Hz), 3.86-3.73 (2H, m), 3.64 (1H, d, 13 Hz), 3.39 (1H, d, 13 Hz), 3.30 (1H, br, s), 2.68 (1H, d, 12 Hz), 2.56 (1H, d, 10 Hz), 2.28-2.15 (2H, m); LCMS: m/z 284 [M+H]+ @ Rt 0.95 min.

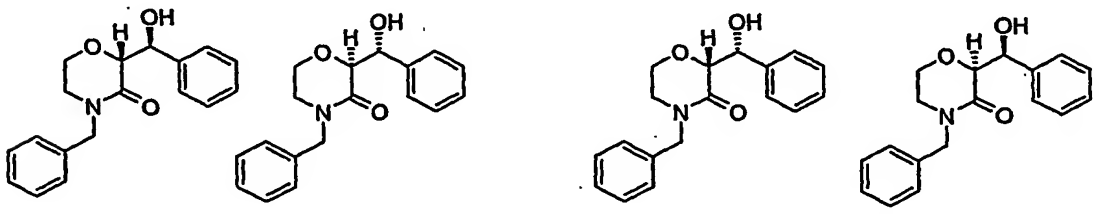
5

(2*S*)-2-[(*R*)-bromo(phenyl)methyl]-4-(phenylmethyl)morpholine (5a)



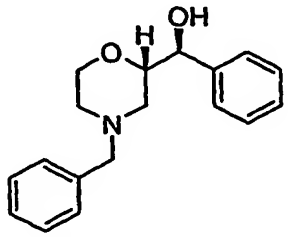
To a solution of **4a** (4.71 g, 16.6 mmol) in anhydrous chloroform (200 ml) under nitrogen was added triphenylphosphine dibromide (14.04 g, 33.26 mmol). The reaction mixture was heated at 60°C overnight. The mixture was allowed to cool to room temperature then washed with saturated aqueous sodium carbonate solution, dried over sodium sulphate and concentrated *in vacuo*. The resulting residue was purified by flash chromatography on silica (eluent: ethyl acetate/isohexane gradient 10/90 to 30/70 [v/v]) to give **5a** as a white solid (4.63 g, 81%); MW 346.27; $C_{18}H_{20}BrNO$; ^1H NMR ($CDCl_3$): 7.14-7.39 (10H, m), 4.83 (1H, d, 7 Hz), 4.01 (1H, br, t, 8 Hz), 3.73 (1H, br, d, 11 Hz), 3.60-3.48 (2H, m), 3.39 (1H, d, 12 Hz), 3.20 (1H, d, 11 Hz), 2.50 (1H, d, 10 Hz), 2.07 (2H, t, 10 Hz); LCMS: (6 min method) m/z 346 [M]+ @ Rt 2.51 min.

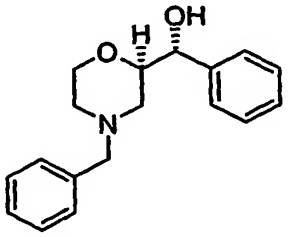
(2*S*)-2-[(*S*)-Hydroxy(phenyl)methyl]-4-(phenylmethyl)morpholin-3-one (6a)
and
(2*S*)-2-[(*R*)-Hydroxy(phenyl)methyl]-4-(phenylmethyl)morpholin-3-one (6b)
and
(2*R*)-2-[(*S*)-Hydroxy(phenyl)methyl]-4-(phenylmethyl)morpholin-3-one (6c)
and
(2*R*)-2-[(*R*)-Hydroxy(phenyl)methyl]-4-(phenylmethyl)morpholin-3-one (6d)



To a stirred solution of **2** (5.02 g, 26 mmol) in anhydrous tetrahydrofuran (25 ml) under nitrogen at -78°C was added lithium diisopropylamide (1.5 eq, 39 mmol, 19.5 ml of a 2M solution in heptane/tetrahydrofuran/ethylbenzene) over approximately 20 minutes, whilst maintaining the reaction temperature below -75°C. The resulting brown solution was stirred for a further 30 minutes at -78°C, before being added over approximately 30 minutes to a solution of benzaldehyde (1.2 eq, 3.29 g, 31 mmol) in anhydrous tetrahydrofuran (15 ml) under nitrogen at -78°C, whilst again maintaining the reaction temperature below -75°C. The resulting yellow solution was stirred at -78°C for 1 hour, before being allowed to warm to room temperature slowly over 1 hour. The reaction mixture was cautiously quenched by addition of saturated ammonium chloride solution (50 ml) and the tetrahydrofuran was evaporated *in vacuo*. The resulting cloudy aqueous solution was extracted with dichloromethane, and the organic extracts were combined, washed with brine, dried over sodium sulphate and the dichloromethane evaporated *in vacuo* to give a thick brown oil (9.2 g), which partially crystallised on standing. After purification by flash column chromatography (eluent: ethyl acetate/dichloromethane 10/90 to 20/80 gradient [v/v]) **6a,6b** was obtained as light red crystals (2.46 g, 32%); MW 297.36; $C_{18}H_{19}NO_3$; ^{1}H NMR ($CDCl_3$): 7.36-7.41 (2H, m), 7.16-7.31 (6H, m), 6.86-6.91 (2H, m), 5.14 (1H, d, J 3 Hz), 4.71 (1H ,d, 14 Hz), 4.48 (1H, d, J 3 Hz), 4.25 (1H, d, 14 Hz), 4.20 (1H, br, s), 3.89 (1H, ddd, 12 Hz, 3 Hz, 2 Hz), 3.67 (1H, dt, 11 Hz, 3 Hz), 3.16 (1H, dt, 12 Hz and 4 Hz), 2.86 (1H, br, d, 12 Hz); LCMS: m/z 298 [M+H]+ @ Rt 1.24 min. **6c, 6d** was isolated as a brown solid (1.42 g) contaminated with **2**. Trituration with ethyl acetate afforded pure **6c,6d** as a white solid (0.484 g, 6%); MW 297.36; $C_{18}H_{19}NO_3$; ^{1}H NMR ($CDCl_3$): 7.55-7.61 (2H, m), 7.36-7.50 (6H, m), 7.25-7.31 (2H, m), 5.21 (1H, d, 2 Hz), 5.09 (1H, d, J 7 Hz and 2 Hz), 4.73 (2H, s), 4.37 (1H, d, J 8 Hz), 4.01 (1H, ddd, 12 Hz, 3 Hz, 2 Hz), 3.77 (1H, dt, 11 Hz, 4 Hz), 3.50 (1H, dt, 12 Hz, 4 Hz), 3.16 (1H, br, d, 12 Hz); LCMS: m/z 298 [M+H]+ @ Rt 1.24 min.

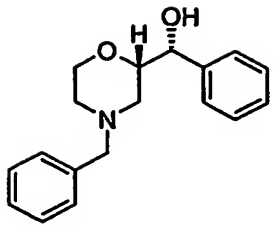
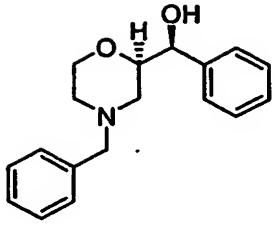
(*S*)-Phenyl[(2*S*)-4-(phenylmethyl)morpholin-2-yl]methanol (4a)
and
(*R*)-Phenyl[(2*R*)-4-(phenylmethyl)morpholin-2-yl]methanol (4b)





To a solution of **6a,6b** (0.033 g, 1.1 mmol) in anhydrous THF (5 ml) under nitrogen at room temperature was slowly added borane (4 eq, 4.4 ml of a 1M solution in tetrahydrofuran, 4.4 mmol). The solution was stirred at 60°C for 2 hours. After cooling down to room temperature, dry methanol (2 ml) was slowly added to quench excess borane reagent. After addition of aqueous hydrochloric acid solution (2 ml of a 1M solution) the reaction mixture was heated to 60°C for 1 hour. The organic solvents were evaporated *in vacuo* and the concentrated solution was poured onto aqueous potassium carbonate solution (10 ml of a 1M solution) and extracted with diethyl ether (2 x 20 ml). The combined organic layers were washed with brine, water, dried over magnesium sulphate and concentrated *in vacuo*. Purification by flash column chromatography (eluent: hexane/ethyl acetate/triethylamine 90/9/1 [v/v/v]) gave a viscous oil (0.19 g, 60%); MW 283.37; $C_{18}H_{21}NO_2$; ^{1}H NMR (CDCl3): 7.45-7.32 (10H, m), 4.67 (1H, d, 7 Hz), 4.03 (1H, dt, 11 Hz, 2.7 Hz), 3.86-3.73 (2H, m), 3.64 (1H, d, 13 Hz), 3.39 (1H, d, 13 Hz), 3.30 (1H, br, s), 2.68 (1H, d, 13 Hz), 2.56 (1H, d, 11 Hz), 2.28-2.15 (2H, m); LCMS: m/z 284 [M+H]+ @ Rt 0.95 min.

(*R*)-[(2*S*)-4-Benzylmorpholinyl](phenyl)methanol (4c)
and
(*S*)-[(2*R*)-4-Benzylmorpholinyl](phenyl)methanol (4d)

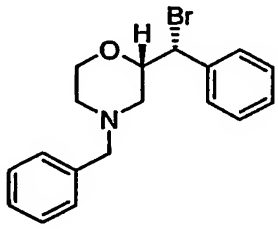
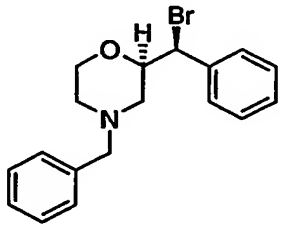



Using the procedure described for the preparation of **4a,4b** starting from **6c,6d** (0.14 g, 0.45 mmol) **4c,4d** was obtained as a viscous oil (0.098 g, 68%); MW 283.37; $C_{18}H_{21}NO_2$; ^1H NMR ($CDCl_3$): 7.17-7.28 (10H, m), 4.80 (1H, d, 4 Hz), 3.88 (1H, dt, 11 Hz, 3 Hz), 3.72 (1H, m), 3.61-3.68 (1H, m), 3.50 (1H, d, 13 Hz), 3.25 (1H, d, 13 Hz), 2.52 (2H, br, t, 12 Hz), 2.17 (1H, t, 11 Hz), 2.08 (1H, td, 11 Hz, 3 Hz); LCMS: m/z 284 [M+H]+ @ Rt 0.98 min.

(2*S*)-2-[(*R*)-Bromo(phenyl)methyl]-4-(phenylmethyl)morpholine (5a)

and

(2*R*)-2-[(*S*)-Bbromo(phenyl)methyl]-4-(phenylmethyl)morpholine (5b)

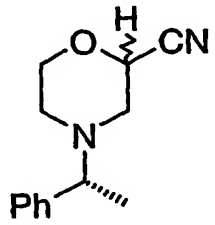
To a solution of **4a,4b** (10.27 g, 36.29 mmol) in anhydrous dichloromethane (150 ml) under nitrogen at room temperature was added freshly recrystallised triphenylphosphine (13.32 g, 50.80 mmol, 1.4 eq) followed by carbon tetrabromide (16.85 g, 50.8 mmol, 1.4 eq) as a solution in anhydrous dichloromethane (50 ml). After 15 minutes the reaction mixture was diluted with dichloromethane (100 ml) and washed with saturated aqueous solution of sodium hydrogencarbonate, brine, dried over magnesium sulphate and concentrated *in vacuo* to give an orange oil (42.0 g). To the orange oil was added diethyl ether (200 ml) and the resulting suspension was sonicated for 30 minutes. The solvent was decanted and the process repeated with a further portion of diethyl ether. The combined organic extracts were concentrated *in vacuo* to yield an orange solid (22.0 g) which was purified by flash column chromatography (eluent: ethyl acetate/hexane/triethylamine 10/89.5/0.5

[v/v/v]) **5a,5b** was otained as a white solid (7.20 g, 57%). Alternative Work-up: The reaction mixture was poured onto a silica (160 g) filtration pad which was washed with dichloromethane (14 x 250 ml). After removal of solvents *in vacuo* and purification by flash column chromatography (eluent: ethyl acetate/hexane/triethylamine gradient 5/94.5/0.5 to 10/89.5/0.5 [v/v/v]) to give a white solid (6.05 g, 48%); MW 346.27; $C_{18}H_{20}BrNO$; ^1H NMR ($CDCl_3$): 7.14-7.39 (10H, m), 4.83 (1H, d, 7 Hz), 4.01 (1H, br, t, 8 Hz), 3.73 (1H, br, d, 11 Hz), 3.48-3.60 (2H, m), 3.39 (1H, d, 12 Hz), 3.20 (1H, d, 11 Hz), 2.50 (1H, d, 10 Hz), 2.07 (2H, t, 11 Hz); LCMS: m/z 348/346 [M+H]+ @ Rt 1.20 min.

4-[(1*R*)-1-Phenylethyl]morpholine-(2*S*)-carbonitrile (47a)

and

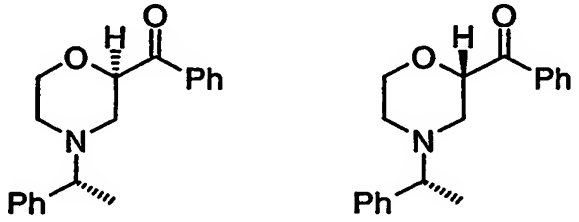
4-[(1*R*)-1-Phenylethyl]morpholine-(2*R*)-carbonitrile (47b)



To (*R*)-(-)-2-hydroxyethyl-α-phenethylamine (1.65 g, 10.0 mmol) in diethyl ether (10ml) was added at room temperature 2-chloroacrylonitrile (0.80 ml, 10.0 mmol) with stirring. The mixture was stirred at room temperature for 4.5 days when additional 2-chloroacrylonitrile (0.8 ml, 10.0 mmol) was added. After stirring another 3.5 days, the reaction mixture was concentrated *in vacuo* to give an oil. The oil was dissolved in dry tetrahydrofurane (30 ml), cooled under nitrogen to 0°C and potassium *tert*-butoxide (1.23 g, 11.0 mmol) added. The solution was stirred at 0°C for 2 hours then at reflux for 1.5 hours, cooled, diluted with diethyl ether and washed with aqueous saturated sodium bicarbonate. The organic phase was extracted with 2N hydrochloric acid and the aqueous made basic by addition of solid sodium bicarbonate and extracted with diethyl ether. The organic phase was dried over magnesium sulphate, filtered and evaporated to a brown oil. The crude product was purified by flash chromatography (eluent: ethyl acetate/hexane gradient 100% ethyl acetate to 50/50 [v/v]) to give **47a,47b** as a colourless oil (0.58g,

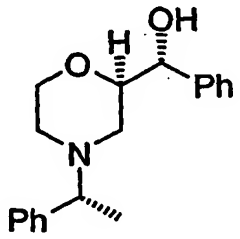
27%%); MW 216.29; $C_{13}H_{16}N_2O$; ^1H NMR ($CDCl_3$) 7.25-7.38 (5H, m), 4.6 (1H, dd), 4.54 (1H, dd), 3.91-4.06 (2H, m), 3.66-3.82 (2H, m), 3.39-3.49 (2H, m), 2.30 - 2. 89 (4H, m), 1.39 (3H, d). *m/z* $[M+H]^+$ 217.

Phenyl{(2*S*)-4-[(1*R*)-1-phenylethyl]morpholin-2-yl}methanone (48a)
and
Phenyl{(2*R*)-4-[(1*R*)-1-phenylethyl]morpholin-2-yl}methanone (48b)



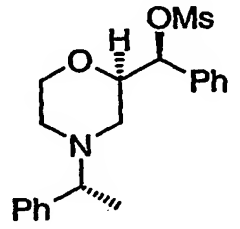
To a stirred solution of **47a,47b** (0.57 g, 2.64 mmol) in dry tetrahydrofurane (10 ml) at 0°C under nitrogen was added a solution of phenylmagnesium chloride in tetrahydrofurane (2.0 M, 2.67 ml) dropwise over 2 minutes. The pale yellow solution was stirred at 0°C for 30 minutes and then allowed to warm to room temperature. After 2 hours the mixture was cooled, quenched with 2M hydrochloric acid and was stirred vigorously for 1 hour at room temperature. After addition of water and extraction with ethyl acetate, the combined organic layers were washed with brine, dried over magnesium sulphate, filtered and evaporated to give an oil (0.63 g). After purification by column chromatography (eluent: ethyl acetate/hexane gradient 0/100 to 20/80 [v/v]) **48a** was obtained as an oil (0.15 g, 19%%); MW 295.38; $C_{19}H_{21}NO_2$; ^1H NMR ($CDCl_3$) 8.00 (2H, d), 7.60 (1H, t), 7.50 (2H, t), 7.20-7.35 (5H, m), 4.96 (1H, d), 3.93-4.00 (1H, m), 3.70-3.80 (1H, m), 3.41 (1H, q), 3.25 (1H, br, d), 2.59 (1H, br, d), 2.13 -2. 36 (2H, m), 1.38 (3H, d). *m/z* $[M+H]^+$ 296 followed by **48b** as an oil (0.27 g, 35%%) ^1H NMR ($CDCl_3$) 7.90 (2H, d), 7.54 (1H, t), 7.45 (2H, t), 7.20-7.38 (5H, m), 4.85 (1H, d), 4.05-4.12 (1H, m), 3.80-3.92 (1H, m), 3.43 (1H, q), 2.86-3.00 (2H, m), 2.29-2.40 (1H, m), 2.21 (1H, t), 1.38 (3H, d). *m/z* $[M+H]^+$ 296.

(*R*)-Phenyl{(2*S*)-4-[(1*R*)-1-phenylethyl]morpholin-2-yl}methanol (50)



To a stirred solution of **48a** (0.08 g, 0.26 mmol) and triphenylsilane (0.34 g, 1.31 mmol) in dichloromethane (4 ml) cooled to 0°C was added boron trifluoride etherate (0.09 g, 0.66 mmol) followed by trifluoroacetic acid (0.36 ml, 63 mmol). The reaction mixture was allowed to warm to room temperature and diluted after three hours with dichloromethane (20 ml) and neutralised with aqueous sodium bicarbonate. The organic phase was dried over magnesium sulphate, filtered and evaporated to give the required product. This was purified as its hydrochloric acid salt crystallising from isopropanol and diethyl ether (0.05 g, 69%%); MW 297.4; $C_{19}H_{23}NO_2$; ^{1}H NMR ($CDCl_3$) on free base 7.08-7.29 (10H, m), 4.78 (1H, d), 3.90-4.00 (1H, m), 3.57-3.68 (2H, m), 3.33 (1H, q), 2.53-2.64 (1H, m), 2.37-2.47 (1H, m), 2.09-2.26 (2H, m), 1.29 (3H, d). *m/z* $[M+H]^+$ 298.

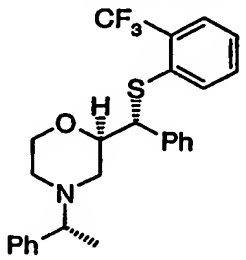
(R)-Phenyl{(2S)-4-[(1R)-1-phenylethyl]morpholin-2-yl}methyl methanesulphonate (51)



To a solution of **50** (0.05 g, 0.17 mmol) in dichloromethane (1 ml) at room temperature was added polymer supported Hünig's base ((Argonaut, 3.56 mmol/g, 0.089 g, 0.32 mmol, 1.9 eq) and methanesulphonyl chloride (0.02 g, 0.19 mmol). The mixture was stirred under nitrogen for 6 hours then filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (eluent: ethyl acetate/heptane 33/67 [v/v]) to give **51** as a colourless oil (0.035 g, 55%%); MW 375.49; $C_{20}H_{25}NO_4S$ ^{1}H NMR ($CDCl_3$) 7.20-7.35 (10H, m), 5.46 (1H, d),

3.79-3.88 (2H, m), 3.59 (1H,td), 3.4 (1H, q), 2.68-2.78 (2H, m), 2.68 (3H, s), 2.03-2.24 (2H, m), 1.34 (3H, d). *m/z* $[M+H]^+$ 376.

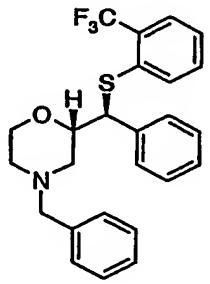
(2S)-4-[(1R)-1-Phenylethyl]-2-((S)-phenyl{[2-(trifluoromethyl)phenyl]thio}methyl)morpholine (52)



A mixture of **51** (0.035 g, 0.093 mmol), potassium carbonate (0.026 g, 0.19 mmol) and 2-trifluoromethylbenzenethiol (0.084 g, 0.47 mmol) in dry, degassed dimethylformamide (0.5 ml) was stirred under nitrogen at room temperature for 3 days. The reaction mixture was diluted with water and extracted with diethyl ether. The extracts was washed with water and brine, dried over magnesium sulphate, filtered and evaporated to give a colourless oil (0.03 g, 71%). Purification by flash column chromatography (eluent: ethyl acetate/heptane 20/80 [v/v]) gave **52** as a colourless oil (0.03 g, 71%); MW 457.56; $C_{26}H_{26}F_3NOS$ ^1H NMR ($CDCl_3$) 7.53 (1H, d), 7.10-7.28 (13H, m), 4.39 (1H, d), 3.85-4.04 (2H, m), 3.8 (1H, td), 3.35 (1H, q), 2.70 (1H, d), 2.40 (1H, d), 2.30 (1H, td), 2.10-2.20 (1H, m), 1.29 (3H, d). *m/z* $[M+H]^+$458.

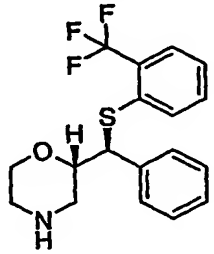
<u>Example 1: (2*S*)-2-((*S*)-Phenyl{[2-(trifluoromethyl)phenyl] thio}methyl) morpholine (9)</u>

(*S*)-Phenyl[(2*S*)-4-(phenylmethyl)morpholin-2-yl]methyl 2-trifluoromethyl)phenyl sulfide (8)



Compound **8** was obtained from **5a** (4.00 g, 11.55 mmol), 2-trifluoromethyl thiophenol (2.47 g, 13.86 mmol, 1.2 eq) and caesium carbonate (4.95 g, 15.24 mmol, 1.1 eq) in dimethylformamide (60 ml) as a brown oil following a modification of **General Procedure 1** in which the reaction was carried out over 1 hour (6.04 g). The oil was purified by flash column chromatography (eluent: hexane/ethyl acetate gradient 100 to 90/10 [v/v]) to give a yellow oil (4.83 g, 94%); MW 443.54; $C_{25}H_{24}F_3NOS$; ^1H NMR ($CDCl_3$): 7.60 (1H, dd, 7 Hz, 1 Hz), 7.17-7.39 (13H, m), 4.50 (1H, d, 7 Hz), 3.97-4.12 (2H, m), 3.73 (1H, dt, 10 Hz, 2 Hz), 3.59 (1H, d, 13 Hz), 3.37 (1H, d, 13 Hz), 2.57-2.68 (2H, m); 2.18-2.38 (2H, m); LCMS (2.5 minute method): m/z 445 [M+H]+ @ Rt 1.50 min.

(2*S*)-2-((*S*)-Phenyl{[2-(trifluoromethyl)phenyl]thio}methyl)morpholine (9)



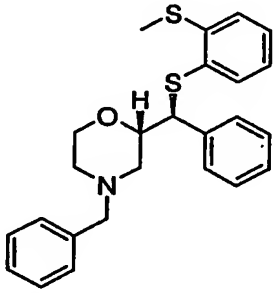
Compound **9** (**Example 1**) was obtained from **8** (5.25 g, 11.84 mmol), solid supported Hünig's base (Argonaut, 3.56 mmol/g, 6.64 g, 23.67 mmol, 2 eq) and α-chloroethyl chloroformate (3.83 ml, 35.51 mmol, 3 eq) in anhydrous dichloromethane (75 ml) following **General Procedure 2**. After evaporation of solvents a light brown solid (5.60 g) was obtained which was recrystallised from iso-propanol. The solid was suspended in ethyl acetate and washed with an aqueous solution of sodium hydroxide (50 ml of a 1M solution). The organic layer was washed with brine, dried over magnesium sulphate and concentrated *in vacuo* to yield the free amine as a colourless oil (3.10 g, 74%); MW 353.41; $C_{18}H_{18}F_3NOS$; ^1H NMR ($CDCl_3$): 7.46 (1H, d, 8 Hz), 7.24 (1H, d, 7 Hz), 7.05-7.2 (7H, m), 4.28 (1H, d, 8 Hz), 3.92 (1H, d, 11 Hz), 3.80 (1H, q, 7 Hz), 3.58 (1H, dt, 2 Hz and 11 Hz), 2.69-2.87 (2H, m), 2.59 (2H, d, 6 Hz), 2.13-1.90 (1H, br s); LCMS (10 minute method): m/z 354 [M+H]+ @ Rt 5.26 min. The hydrochloride salt of **9** was obtained following **General Procedure 3**.

An alternative method for the preparation of compound **9** (**Example 1**), according to Scheme 6, is as follows:

To a suspension of polymer supported Hünig's base (0.11 g, 0.40 mmol) and **52** (0.03 g, 0.066 mmol) in dry dichloromethane (1 ml) was added α-chloroethyl chloroformate (0.09 g, 0.066 mmol) at room temperature under nitrogen. The mixture was stirred at room temperature over the weekend then filtered and concentrated *in vacuo*. This was taken up in methanol, heated at 70°C for 2 hours, cooled, and purified by SCX chromatography (eluent: ammonia/methanol 1/1 [v/v]) to give **9** as a colourless oil (0.01 g, 43%). The spectroscopic data for **9** obtained by the route outlined here was identical to the data for **9** obtained as described above.

Example 2: (2*S*)-2-((*S*)-Phenyl{[2-(thiomethyl)phenyl]thio}methyl) morpholine (11)

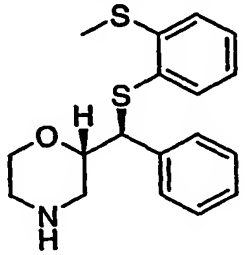
(2*S*)-2-[(*S*)-{[2-(methylthio)phenyl]thio}(phenyl)methyl]-4-(phenylmethyl)morpholine (10)



Compound **10** was obtained from **5a** (4.0 g, 11.55 mmol), 2-methylsulphenyl-thiophenol (2.17 g, 13.86 mmol, 1.2 eq) and caesium carbonate (4.42 g, 13.63 mmol, 1.18 eq) in dimethylformamide (35 ml) following a modification of **General Procedure 1** in which the mixture was heated at 50°C for 1.5 hours, allowed to cool to room temperature, taken up in methanol and treated with SCX-2 (100 g). The SCX-2 was washed with methanol. **10** was obtained as a white solid (4.92 g) after SCX chromatography (eluent: ammonia/methanol 1/1 [v/v]) and removal of solvents *in vacuo*. Purification by flash column chromatography (eluent: ethyl acetate/isohexane gradient 10/90 to 30/70 [v/v]) gave **10** as a white solid (4.04 g, 83%); MW 421.63; $C_{27}H_{27}NOS_2$; ^1H NMR ($CDCl_3$): 7.03-7.15 (6H, m), 6.93-6.99 (2H, m), 6.74 (1H, td, 7 Hz, 1 Hz), 4.31 (1H, d, 8 Hz),

3.95 (1H, br, d, 12 Hz), 3.83 (1H, td, 8 Hz, 3.8 Hz), 3.59 (1H, td, 11 Hz and 3 Hz), 2.82 (1H, td, 12 Hz and Hz), 2.61-2.75 (3H, m), 2.35 (3H, s), 1.73 (1H, br, s); LCMS (6 minute method): m/z 422 [M+H]+ @ Rt 3.36 min.

(2*S*)-2-((*S*)-Phenyl{[2-(trifluoromethyl)phenyl]thio}methyl)morpholine (11)



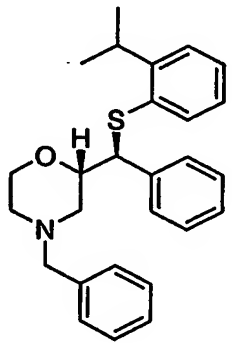
Compound **11** **(Example 2)** was obtained from **10** (4.02 g, 9.53 mmol), solid supported Hünig's base (Argonaut, 3.56 mmol/g, 5.02 g, 17.87 mmol, 2 eq) and α-chloroethyl chloroformate (3.09 ml, 28.6 mmol, 3 eq) in anhydrous dichloromethane (75 ml) following **General Procedure 2**. The mixture was heated at 40°C for 1.5 hours then left to stir at room temperature overnight. The reaction mixture was filtered and concentrated *in vacuo* to give a pale orange liquid. This was taken up in methanol (70 ml) and heated at 40°C for 2 hours. A white solid crashed out of the solution which was taken up in methanol and purified by SCX chromatography (eluent: ammonia/methanol 1/1 [v/v]). After evaporation *in vacuo* **11** was obtained as a pale yellow oil (3.13 g, 99%); MW 331.50; $C_{18}H_{21}NOS_2$; ^1H NMR ($CDCl_3$): 7.03-7.15 (6H, m), 6.93-6.99 (2H, m), 6.74 (1H, td, 7 Hz, 2 Hz), 4.31 (1H, d, 8 Hz), 3.95 (1H, br, d, 12 Hz), 3.83 (1H, td, 8 Hz, 4 Hz), 3.59 (1H, td, 11 Hz, 3 Hz), 2.82 (1H, td, 12 Hz, 3 Hz), 2.61-2.75 (3H, m), 2.35 (3H, s), 1.73 (1H, br, s). Compound **11** was converted into its hydrochloride salt following a modification of **General Procedure 3** in which the pale yellow oil was taken up in isopropanol (~200 ml) and filtered. Addition of hydrogen chloride (19 ml of a 1M solution in diethyl ether, 19 mmol) gave a white precipitate to which further diethyl ether (~50 ml) was added. The solid was isolated by filtration and washed with diethyl ether to give the hydrochloride salt of **11** as a white solid (3.03 g, 78%); MW 367.96; $C_{18}H_{22}ClNOS_2$; ^1H NMR ($CDCl_3$): 9.94 (2H, br, s), 7.06-7.18 (6H, m), 6.94-7.03 (2H, m), 6.78 (1H, t, 7 Hz), 4.24-4.32 (1H, m), 4.20 (1H, d, 6 Hz), 3.89-

4.06 (2H, m), 3.18 (2H, br, t, 12 Hz), 2.99 (2H, br, s), 2.37 (3H, s); LCMS (10 minute method): m/z 332 [M-HCl]+ @ Rt 5.07 min.

Example 3:

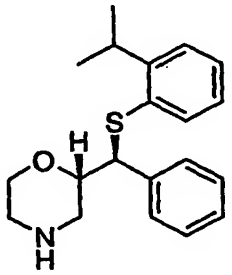
(2*S*)-2-[(*S*)-{[2-(1-methylethyl)phenyl]thio}(phenyl)methylmorpholine (13)

(2*S*)-2-[(*S*)-{[2-(1-methylethyl)phenyl]thio}(phenyl)methyl]-4-(phenylmethyl)morpholine (12)



Compound **12** was obtained from **5a** (4.04 g, 11.66 mmol), 2-isopropylsulphenyl-thiophenol (2.35 ml, 14 mmol, 1.2 eq) and caesium carbonate (4.56 g, 14 mmol, 1.2 eq) in dimethylformamide (35 ml) following a modification of **General Procedure 1** in which the mixture was heated at 90°C for 20 minutes, allowed to cool to room temperature, taken up in ethyl acetate (50 ml), washed with water and brine, dried over sodium sulphate, filtered and reduced *in vacuo* to give a yellow oil which was purified by SCX chromatography (eluent: ammonia/methanol 1/1 [v/v]). Removal of solvents *in vacuo* gave **12** as a white solid (4.45, 91%); MW 417.62; $C_{27}H_{31}NOS$; ^1H NMR ($CDCl_3$): 7.14-7.26 (7H, m), 7.03-7.1 (6H, m), 6.86-6.92 (1H, m), 4.10 (1H, d, 8 Hz), 3.88-3.94 (2H, m), 3.62 (1H, td, 11 Hz, 2 Hz), 3.37-3.47 (2H, m), 3.22 (1H, d, 13 Hz), 2.50 (2H, d, 11 Hz), 2.12-2.29 (2H, m), 1.05 (3H, d, 7 Hz), 0.92 (3H, d, 7 Hz); LCMS (6 minute method): m/z 418 [M+H]+ @ Rt 3.72 min.

(2*S*)-2-[(*S*)-{[2-(1-methylethyl)phenyl]thio}(phenyl)methyl]morpholine (13)

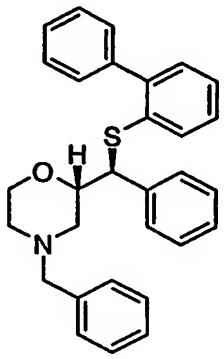


Compound **13** (**Example 3**) was obtained from **12** (4.44 g, 10.65 mmol), solid supported Hünig's base (Argonaut, 3.56 mmol/g, 6.05 g, 21.54 mmol, 2 eq) and α-chloroethyl chloroformate (3.30 ml, 32.0 mmol, 3 eq) in anhydrous dichloromethane (50 ml) following **General Procedure 2**. The mixture was heated at 40°C for 1.5 hours then left to stir at room temperature overnight. The reaction mixture was filtered and concentrated *in vacuo* to give a pale yellow liquid. This was taken up in methanol (50 ml) and heated at 60°C for 1.5 hours. The reaction mixture was allowed to cool to room temperature and purified by SCX chromatography (eluent: ammonia/methanol 1/1 [v/v]) to give **13** as a pale yellow oil; MW 327.49; $C_{20}H_{25}NOS$; ^{1}H NMR ($CDCl_3$): 7.22 (1H, d, 8 Hz), 7.03-7.13 (7H, m), 6.87-6.92 (1H, m), 4.04 (1H, d, 8 Hz), 3.94-3.99 (1H, m), 3.79 (1H, td, 9 Hz, 3 Hz), 3.61 (1H, td, 11 Hz, 3 Hz), 3.41 (1H, sept., 7 Hz), 2.82 (1H, td, 12 Hz and 3 Hz), 2.72 (1H, br, d, 12 Hz), 2.52-2.63 (2H, m), 1.70 (1H, br, s), 1.05 (3H, d, 7 Hz), 0.91 (3H, d, 7 Hz). Compound **13** was converted into its hydrochloride salt following a modification of **General Procedure 3** in which the pale yellow oil was taken up in ether (50 ml), and filtered. Addition of hydrogen chloride in dry diethyl ether (19 ml of a 1M solution in diethyl ether) gave a white precipitate to which further diethyl ether (50 ml) was added. The reaction mixture was concentrated and the residue washed with diethyl ether to give a white solid (2.76 g, 69% overall yield from **5a**); MW 363.95; $C_{20}H_{25}NOS.HCl$; ^{1}H NMR ($CDCl_3$): 9.91 (2H, br, s), 7.05-7.22 (7H, m), 6.91-6.96 (2H, m), 4.23-4.31 (1H, m), 4.08-3.90 (3H, m), 3.31-3.41 (1H, m), 3.04-3.21 (2H, br, m), 2.91-2.99 (2H, br, m), 1.06 (3H, d, 7 Hz), 0.93 (3H, d, 7 Hz); LCMS (10 minute method): m/z 327 [M-HCl]+ @ Rt 5.7 min.

Example 4:

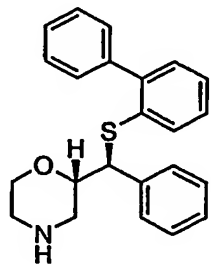
(2*S*)-2-[(*S*)-([1,1'-Biphenyl]-2-ylthio)(phenyl)methyl]morpholine (15)

(2*S*)-2-[(*S*)-([1,1'-Biphenyl]-2-ylthio)(phenyl)methyl]-4-(phenylmethyl)morpholine (14)



Compound **14** was obtained from **5a** (2.16 g, 6.24 mmol), 2-phenylsulphenyl-thiophenol (2.35 ml, 14 mmol, 1.2 eq) and caesium carbonate (2.43 g, 7.5 mmol, 1.2 eq) in dimethylformamide (50 ml) following a modification of **General Procedure 1** in which the mixture was heated at 90°C for 20 minutes, allowed to cool to room temperature, taken up in ethyl acetate (50 ml), washed with water and brine, dried over sodium sulphate, filtered and reduced *in vacuo* to give a yellow oil. Purification by SCX-chromatography (eluent: ammonia/methanol 1/1 [v/v]) followed by evaporation *in vacuo* gave **14** as a white solid (0.59 g, 90%); MW 451.64; $C_{30}H_{29}NOS$; ^1H NMR ($CDCl_3$): 6.93-7.34 (19H, m), 3.92 (1H, br, d, 6 Hz), 3.63-3.76 (2H, m), 3.45 (1H, t, 10 Hz), 3.33 (1H, d, 13 Hz), 3.17 (1H, d, 12 Hz), 2.39 (1H, d, 12 Hz), 2.20 (1H, d, 11 Hz), 1.97-2.07 (1H, m), 1.82-1.92 (1H, m); LCMS (6 minute method): m/z 452 [M+H]+ @ Rt 3.69 min.

(2*S*)-2-[(*S*)-([1,1'-Biphenyl]-2-ylthio)(phenyl)methyl]morpholine (15)



Compound **15** (**Example 4**) was obtained from **14** (2.95 g, 6.54 mmol), solid supported Hünig's base (Argonaut, 3.56 mmol/g, 13.06 g, 21.54 mmol, 2 eq) and α-chloroethyl chloroformate (2.0 ml, 19.6 mmol, 3 eq) in anhydrous dichloromethane (50 ml) following **General Procedure 2**. The reaction mixture was concentrated *in vacuo* to give a pale yellow liquid. This was taken up in methanol (70 ml) and heated at 40°C for 2 hours. A white solid crashed out of the solution which was taken up in methanol and purified by SCX-chromatography (eluent: ammonia/methanol 1/1 [v/v]). After removal of solvents *in vacuo* **15** was obtained as a pale yellow oil; MW 361.51; $C_{23}H_{23}NOS$; ^1H NMR ($CDCl_3$): 7.0-7.45 (14H, m), 3.95 (1H, d, 8 Hz), 3.65-3.85 (2H, m), 3.35 (1H, d, 12 Hz), 3.2 (1H, d, 12 Hz), 2.45 (1H, d, 10 Hz), 2.20 (1H, d, 10 Hz), 2.0-2.15 (1H, m), 1.8-2.0 (1H, m); LCMS (12 minute method): m/z 363 [M+H]+ @ Rt 3.00 min. **15** was converted into its hydrochloride salt following a modification of **General Procedure 3** in which the pale yellow oil was taken up in isopropanol (~200 ml), and filtered. Addition of hydrogen chloride (19 ml of a 1M solution in diethyl ether) gave a white precipitate to which further diethyl ether (~50 ml) was added. The solid was isolated by filtration and washed with diethyl ether to give the hydrochloride salt of **15** as a white solid (1.95 g, 75% overall yield from **5a**); MW 397.97; $C_{23}H_{23}NOS.HCl$; ^1H NMR ($CDCl_3$): 9.80 (2H, br, s), 7.38-7.03 (12H, m), 6.90-6.96 (2H, m), 3.85-4.00 (2H, m), 3.72-3.82 (1H, m), 3.66 (1H, d, 5 Hz), 2.98-3.10 (1H, m), 2.81 (1H, br, s), 2.62 (2H, br, s); LCMS (12 minute method): m/z 362 [M+H]+ @ Rt 2.99 min.

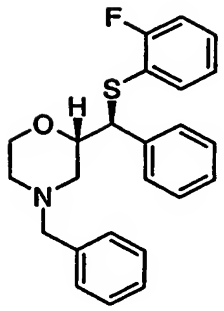
Example 5:

(2*S*)-2-[(*S*)-[(2-Fluorophenyl)thio](phenyl)methyl]morpholine (17)

(2*S*)-2-[(*S*)-[(2-Fluorophenyl)thio](phenyl)methyl]-4-phenylmethyl)morpholine (16a)

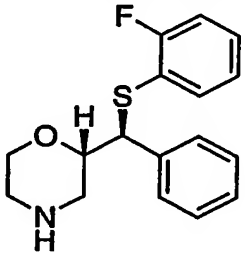
and

(2*R*)-2-[(*R*)-[(2-Fluorophenyl)thio](phenyl)methyl]-4-phenylmethyl)morpholine (16b)



Compounds **16a,16b** were obtained from **5a,5b** (0.114 g, 0.33 mmol), 2-fluorothiophenol (0.045 g, 0.36 mmol, 1.2 eq) and caesium carbonate (0.12 g, 0.36 mmol, 1.2 eq) in dimethylformamide (50 ml) following **General Procedure 1** as a pale yellow oil (0.14 g, 65%); MW 393.53; $C_{24}H_{24}FNOS$; ^1H NMR ($CDCl_3$): 7.12-7.36 (12H, m), 6.87-6.99 (2H, m), 4.48 (1H, d, 8 Hz), 4.00-4.11 (2H, m), 3.77 (1H, td, 11 Hz, 2 Hz), 3.60 (1H, d, 13 Hz), 3.37 (1H, d, 13 Hz); 2.63 (2H, t, 10 Hz), 2.16-2.31 (2H, m); LCMS (2.5 minute method): *m/z* 394 $[M+H]^+$ @ R_t 1.41 min.

(2*S*)-2-[(*S*)-[(2-Fluorophenyl)thio](phenyl)methyl]morpholine (17)



Compound **17** (**Example 5**) was obtained from **16a,16b** (0.72 g, 0.18 mmol), solid supported Hünig's base (Argonaut, 3.56 mmol/g, 2.0 g, 0.56 mmol, 3 eq) and α-chloroethyl chloroformate (0.62 ml, 0.56 mmol, 3 eq) in anhydrous dichloromethane (5 ml) following **General Procedure 2** as a viscous yellow oil (0.046 g, 82%) from which **17** was obtained as a single isomer after separation by chiral HPLC (0.016 g); Chiral LC (AD): 10.83 min. LC purity = 91% (UV254nm) / 98% (ELS); LCMS (10 minute method): m/z 304 [M+H]+ @ Rt 5.82 min; HPLC purity = 84% (UV215nm) / 98% (ELS); MW 303.41; $C_{17}H_{18}FNOS$; ^1H NMR ($CDCl_3$): 7.13-7.00 (7H, m), 6.87-6.76 (2H, m), 4.29 (1H, d, 9 Hz), 3.98-3.93, (1H, m), 3.78 (1H, td, 9 Hz and 4 Hz), 3.60 (1H, td, 11 Hz and 3 Hz), 2.82 (1H, td, 12 Hz, 3 Hz), 2.76-2.70 (1H, m), 2.57-2.53, (2H, m), NH signal not observed; LCMS

(10 minute method): m/z 304 [M+H]+ @ Rt 5.84 min; HPLC purity = 100%% (ELS). Compound **17** was converted into its hydrochloride salt following **General Procedure 3.**

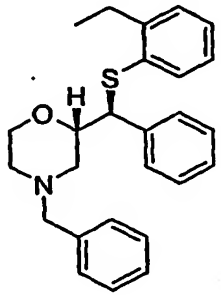
Example 6:

(2*S*)-2-[(*S*)-[(2-Ethylphenyl)thio](phenyl)methyl]morpholine (19)

(2*S*)-2-[(*S*)-[(2-Ethylphenyl)thio](phenyl)methyl]-4-(phenylmethyl)morpholine (18a)

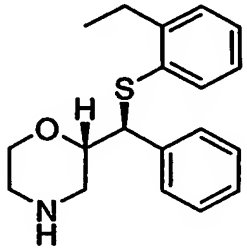
and

(2*R*)-2-[(*R*)-[(2-Ethylphenyl)thio](phenyl)methyl]-4-(phenylmethyl)morpholine (18b)



Compounds **18a,18b** were obtained from **5a,5b** (0.2 g, 0.58 mmol), 2-ethylthiophenol (0.16 g, 1.16 mmol, 2 eq) and caesium carbonate (0.23 g, 0.7 mmol, 1.2 eq) in dimethylformamide (5 ml) following modification of **General Procedure 1** in which the reaction mixture was heated to 95°C for 2 hours. After purification by flash column chromatography (eluent: ethyl acetate/hexane 9/1 [v/v]) **18a,18b** was obtained as a white solid (0.15 g, 65%%); MW 403.59; $C_{26}H_{29}NOS$; ^1H NMR ($CDCl_3$): 6.96-7.40 (14H, m), 4.22 (1H, d, 7 Hz), 3.96-4.01 (2H, m), 3.72 (1H, td, 11 Hz and 2 Hz), 3.52 (1H, d, 13 Hz), 3.32 (1H, d, 13 Hz), 2.68 (2H, q, 8 Hz), 2.59 (2H, br d, 12 Hz), 2.06-2.21 (2H, m), 1.12 (3H, t, 7 Hz); LCMS (2.5 minute method) m/z 404 [M+H]+ @ Rt 1.49 min.

(2*S*)-2-[(*S*)-[(2-Ethylphenyl)thio](phenyl)methyl]morpholine (19)



Compound **19** (**Example 6**) was obtained from **18a,18b** (0.18 g, 0.52 mmol), solid supported Hünig's base (Argonaut, 3.56 mmol/g, 3.7 g, 1.04 mmol, 2 eq) and α-chloroethyl chloroformate (0.34 ml, 3.12 mmol, 3 eq) in anhydrous dichloromethane (5 ml) following **General Procedure 2** as a viscous yellow oil (0.21 g, 86%) from which **19** was obtained after separation by chiral HPLC on chiral OD semi-preparative column; chiral LC (OD): 15.95 min. LC purity = 100% (UV254nm) / 100% (ELS); MW 313.47; $C_{19}H_{23}NOS$; ^1H NMR ($CDCl_3$): 7.17 (1H, d, 8 Hz), 7.12-7.05 (5H, m), 7.01 (2H, d, 4 Hz), 6.87-6.93 (1H, m), 4.07 (1H, d, 8 Hz), 3.92-3.97 (1H, m), 3.74-3.80 (1H, m), 3.59 (1H, td, 11 Hz, 3 Hz), 2.80 (1H, td, 12 Hz and 3 Hz), 2.71 (1H, br, d, 12 Hz), 2.63-2.54 (4H, m), 1.64 (1H, br, s), 1.04 (3H, t, 8 Hz); LCMS (10 minute method): m/z 314 [M+H]+ @ Rt 5.92 min. **19** was converted into its hydrochloride salt following **General Procedure 3**; MW 349.93; $C_{19}H_{23}NOS.HCl$; ^1H NMR ($CDCl_3$): 10.10 (2H, br, s), 7.13-7.28 (8H, m), 7.02-7.08 (1H, m), 4.36 (1H, br, s), 4.01-4.17 (3H, br, m), 3.16-3.31 (2H, br, m), 2.92-3.09 (2H, br, m), 2.71 (2H, q, 8 Hz), 1.15 (3H, t, 7 Hz).

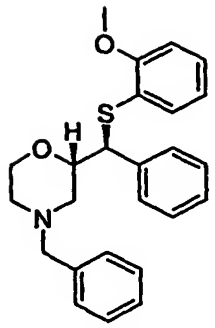
Example 7:

(2*S*)-2-[(*S*)-{[2-(Methyloxy)phenyl]thio}(phenyl)methyl]morpholine (21)

(2*S*)-2-[(*S*)-{[2-(Methyloxy)phenyl]thio}(phenyl)methyl]-4-(phenylmethyl)morpholine (20a)

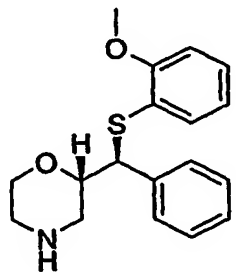
and

(2*R*)-2-[(*R*)-{[2-(Methyloxy)phenyl]thio}(phenyl)methyl]-4-(phenylmethyl)morpholine (20b)



Compounds **20a,20b** were obtained from **5a,5b** (0.18 g, 0.52 mmol), 2-methoxy thiophenol (0.074 ml, 0.57 mmol, 1.2 eq) and caesium carbonate (0.17 g, 0.52 mmol, 1.2 eq) in dimethylformamide (5 ml) following modification of **General Procedure 1** in which the reaction was heated at 95°C for 2.5 hours. After purification by flash column chromatography (eluent: ethyl acetate/hexane gradient 15/85 to 25/75 [v/v]) **20a,20b** was obtained as a viscous yellow oil (0.17 g, 83%); MW 405.56; $C_{25}H_{27}NO_2S$; ^1H NMR ($CDCl_3$): 7.01-7.26 (12H, m), 6.58-6.63 (2H, m), 4.39 (1H, d, 7 Hz), 3.86-3.91 (2H, m), 3.71 (3H, s), 3.56-3.62 (1H, m), 3.42 (1H, d, 11 Hz); 3.21 (1H, d, 11 Hz), 2.46-2.52 (2H, m), 2.01-2.11 (2H, m); LCMS (10 minute method): *m/z* 406 $[M+H]^+$ @ R_T 6.09 min.

(2*S*)-2-[(*S*)-{[2-(Methyloxy)phenyl]thio}(phenyl)methyl]morpholine (21)



Compound **21** (**Example 7**) was obtained from **20a,20b** (0.1 g, 0.25 mmol), solid supported Hünig's base (Argonaut, 3.56 mmol/g, 1.78 g, 0.5 mmol, 2 eq) and α-chloroethyl chloroformate (0.16 ml, 1.5 mmol, 3 eq) in anhydrous dichloromethane (5 ml) following **General Procedure 2** as a viscous yellow oil (0.06 g, 77%) from which **21** was obtained after separation by chiral HPLC on a Chiralcel OJ semi-preparative column. Chiral LC: 11.45 min. LC purity = 100%; MW 315.44; $C_{18}H_{21}NO_2S$; ^1H NMR ($CDCl_3$): 7.14-7.34 (7H, m), 6.74-6.84 (2H,

m), 4.50 (1H, d, 8 Hz), 4.10 (1H, d, 11 Hz), 3.85-4.00 (4H, m), 3.74 (1H, dt, 1 Hz, 11 Hz), 2.82-3.02 (2H, m), 2.66-3.02 (3H, m); LCMS (10 minute method): *m/z* 316 $[M+H]^+$ @ R_t 4.87 min. **21** was converted its hydrochloride salt following **General Procedure 3.**

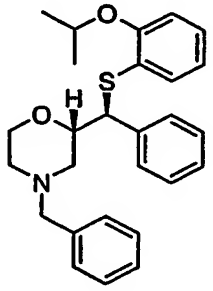
Example 8:

(2*S*)-2-[(*S*)-({2-[(1-Methylethyl)oxy]phenyl}thio)(phenyl)methyl]morpholine (23)

(2*S*)-2-[(*S*)-({2-[(1-Methylethyl)oxy]phenyl}thio)(phenyl)methyl]-4-(phenylmethyl)morpholine (22a)

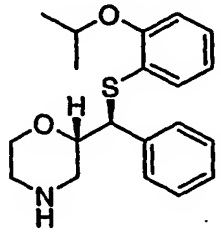
and

(2*R*)-2-[(*R*)-({2-[(1-Methylethyl)oxy]phenyl}thio)(phenyl)methyl]-4-(phenylmethyl)morpholine (22b)



Compounds **22a,22b** were obtained from **5a,5b** (0.57 g, 1.7 mmol), 2-isopropoxy-thiophenol (0.94 g, 5.61 mmol) and caesium carbonate (2.18 g, 6.72 mmol, 1.2 eq) in dimethylformamide (15 ml) following modification of **General Procedure 1** in which the reaction mixture was heated to 95°C for 3 hours. After purification by SCX chromatography (eluent: ammonia/methanol 1/1 [v/v]) **22a,22b** was obtained as a dark yellow oil (0.56 g, 76%%); MW 433.62; $C_{27}H_{31}NO_2S$; ^1H NMR ($CDCl_3$): 7.01-7.24 (7H, m), 6.94-7.09 (5H, m), 6.64 (1H, d, 8 Hz), 6.56 (1H, td, 8 Hz, 1 Hz), 4.42-4.51 (2H, m), 3.83-3.92 (2H, m), 3.56 (1H, td, 11 Hz and 3 Hz), 3.42 (1H, d, 13 Hz), 3.24 (1H, d, 13 Hz), 2.52 (1H, d, 11 Hz), 2.46 (1H, d, 11 Hz), 2.05-2.17 (2H, m), 1.29 (3H, d, 6 Hz), 1.27 (3H, d, 6 Hz); LCMS (2.5 minute method): *m/z* 434 $[M+H]^+$ @ R_T 1.44 min.

(2*S*)-2-[(*S*)-({2-[(1-Methylethyl)oxy]phenyl}thio)(phenyl)methyl]morpholine (23)



Compound **23** (**Example 8**) was obtained from **22a,22b** (0.56 g, 1.3 mmol), solid supported Hünig's base (Argonaut, 3.56 mmol/g, 0.73 g, 2.6 mmol, 2 eq) and α-chloroethyl chloroformate (0.16 ml, 1.5 mmol, 3 eq) in anhydrous dichloromethane (5 ml) following **General Procedure 2** as a viscous yellow oil (0.41 g, 93%) after separation using chiral HPLC on a OD semi-preparative column. Chiral LC (OD): 12.51 min. LC purity = 100% (UV254nm) / 100% (ELS); MW 343.49; $C_{20}H_{25}NO_2S$; ^1H NMR ($CDCl_3$): 7.13-7.20 (1H, m), 6.96-7.12 (6H, m), 6.67 (1H, d, 8 Hz), 6.59 (1H, td, 7 Hz, 1 Hz), 4.48 (1H, sept., 6 Hz), 4.38 (1H, d, 7 Hz), 3.90-3.95 (1H, m), 3.73 (1H, td, 8 Hz, 4 Hz), 3.54 (1H, td, 11 Hz and 3 Hz), 2.79 (1H, td, 12 Hz and 3 Hz), 2.62-2.72 (3H, m), 1.55 (1H, br, s), 1.32 (3H, d, 6 Hz), 1.29 (3H, d, 6 Hz); LCMS (10 minute method): m/z 344 [M+H]+ @ Rt 6.19 min; HPLC purity = 92% (UV215nm). **23** was converted into its hydrochloride salt following **General Procedure 3**; MW 379.95; $C_{20}H_{25}NO_2S.HCl$; ^1H NMR ($CDCl_3$): 9.81-10.04 (2H, br, m), 7.03-7.25 (7H, m), 6.71 (1H, d, 8 Hz), 6.63 (1H, t, 7 Hz), 4.51 (1H, sept., 6 Hz), 4.31 (1H, d, 6 Hz), 4.15-4.23 (1H, m), 3.83-4.03 (2H, m), 3.05-3.18 (2H, m), 2.80-3.03 (2H, m), 1.31 (3H, d, 6 Hz), 1.29 (3H, d, 6 Hz).

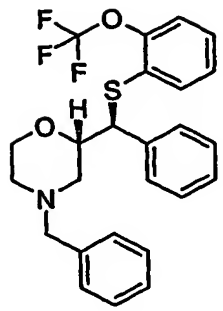
Example 9:

2-{[(*S*)-(2*S*)-Morpholin-2-yl(phenyl)methyl]thio}phenyl trifluoromethyl ether (25)

(2*S*)-4-(Phenylmethyl)-2-[(*S*)-phenyl({2-[(trifluoromethyl)oxy]phenyl}thio)methyl]morpholine (24a)

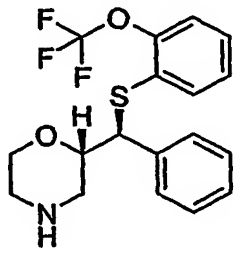
and

(2*S*)-4-(Phenylmethyl)-2-[(*S*)-phenyl({2-[(trifluoromethyl)oxy]phenyl}thio)methyl]morpholine (24b)



Compounds **24a,24b** were obtained from **5a,5b** (0.011 g, 0.33 mmol), 2-trifluoromethoxythiophenol (1.2 eq, 0.077g, 0.39 mmol) and caesium carbonate (0.15 g, 0.47 mmol, 1.2 eq) in dimethylformamide (15 ml) following modification of **General Procedure 1** in which the reaction was heated at 95°C for 1.5 hours. The reaction mixture was allowed to cool to room temperature, diluted with ethyl acetate (20 ml), washed sequentially with water and brine, dried over sodium sulphate and finally concentrated *in vacuo* to give a pale yellow oil (0.14 g, 92%); MW 459.53; $C_{25}H_{24}F_3NO_2S$; ^{1}H NMR ($CDCl_3$): 7.13-7.41 (13H, m), 7.08-7.13 (1H, m), 4.51 (1H, d, 8 Hz), 3.99-4.07 (2H, m), 3.73 (1H, td, 9 Hz, 2.5 Hz), 3.57 (1H, d, 13 Hz), 3.37 (1H, d, 13 Hz); 2.57-2.66 (2H, m), 2.20-2.31 (2H, m); LCMS (10 minute method): *m/z* 460 $[M+H]^+$ @ R_t 6.69 min.

2-{[(*S*)-(2*S*)-Morpholin-2-yl(phenyl)methyl]thio}phenyl trifluoromethyl ether (25)



Compound **25** (**Example 9**) was obtained from **24a,24b** (0.06 g, 0.13 mmol), solid supported Hünig's base (Argonaut, 3.56 mmol/g, 0.073 g, 0.026 mmol, 2 eq) and α-chloroethyl chloroformate (0.04 ml, 0.39mmol, 3 eq) in anhydrous dichloromethane (5 ml) following **General Procedure 2** as a viscous yellow oil (0.021 g, 44%) from which **25** was obtained after separation using chiral HPLC on a OD semi-preparative column. Chiral LC (OJ): 12.60 min. LC purity =

98% (UV_{254nm}) / 100% (ELS); MW 369.41; $C_{18}H_{18}F_3NO_2S$; ^1H NMR ($CDCl_3$): 7.02-7.21 (8H, m), 6.91-6.96 (1H, m), 4.28 (1H, d, 8 Hz), 3.93 (1H, br, d 11 Hz), 3.75-3.81 (1H, m), 3.60 (1H, td, 11 Hz and 3 Hz), 2.71-2.86 (2H, m), 2.61 (2H, d, 6 Hz), 1.90 (1H br, s); LCMS (10 minute method): *m/z* 370 $[M+H]^+$ @ R_t 5.86 min.

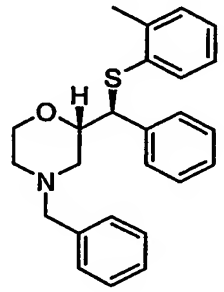
Example 10:

(2*S*)-2-[(*S*)-[(2-Methylphenyl)thio](phenyl)methyl]morpholine (27)

(2*S*)-2-[(*S*)-[(2-Methylphenyl)thio](phenyl)methyl]-4-(phenylmethyl)morpholine (26a)

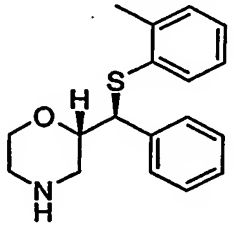
and

(2*R*)-2-[(*R*)-[(2-Methylphenyl)thio](phenyl)methyl]-4-(phenylmethyl)morpholine (26b)



Compounds **26a,26b** were obtained from **5a,5b** (0.1 g, 0.29 mmol), 2-methyl thiophenol (0.04 ml, 0.31 mmol) and caesium carbonate (0.125 g, 0.37 mmol, 1.2 eq) in dimethylformamide (15 ml) following **General Procedure 1** as a colourless oil (0.13 g, 85%); MW 389.56; $C_{25}H_{27}NOS$; ^1H NMR ($CDCl_3$): 6.84-7.24 (14H, m), 4.14 (1H, d, 8 Hz), 3.85-3.95 (2H, m), 3.60 (1H, dt, 10 Hz, 3 Hz), 3.42 (1H, d, 13 Hz); 3.21 (1H, d, 13 Hz), 2.46-2.54 (2H, m), 2.18 (3H, s), 1.97-2.13 (2H, m); LCMS (2.5 minute method): *m/z* 390 $[M+H]^+$ @ R_T 1.49 min.

(2*S*)-2-[(*S*)-[(2-Methylphenyl)thio](phenyl)methyl]morpholine (27)

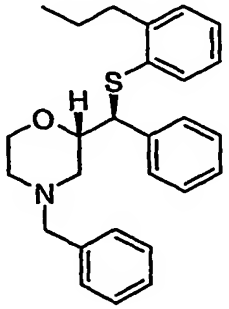


Compound **27** **(Example 10)** was obtained from **26a,26b** (0.04 g, 0.12 mmol), solid supported Hünig's base (Argonaut, 3.56 mmol/g, 0.89 g, 0.24 mmol, 2 eq) and α-chloroethyl chloroformate (0.04 ml, 0.36mmol, 3 eq) in anhydrous dichloromethane (5 ml) following **General Procedure 2** as a viscous yellow oil (0.03 g, 75%) from which **27** was obtained after chiral separation. Chiral LC (OJ): 15.84 min. LC purity = 98.57% (UV_{254nm}); MW 299.44; $C_{18}H_{21}NOS$; ^1H NMR ($CDCl_3$): 6.86-7.21 (9H, m), 4.08 (1H, d, 7 Hz), 3.75 (1H, br s), 3.58 (1H, br s), 2.34-3.1 (4H, m), 2.20 (3H, s); 1.41-2.04 (2H, m); LCMS (10 minute method): *m/z* 300 $[M+H]^+$ @ R_T 5.08 min. **27** was converted into its hydrochloride salt following **General Procedure 3.**

Example 11:

(2*S*)-2-{(*S*)-Phenyl[(2-propylphenyl)thio]methyl}morpholine (29)

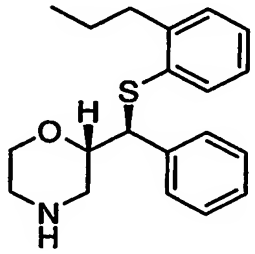
(*S*)-Phenyl[(2*S*)-4-(phenylmethyl)morpholin-2-yl]methyl-2-propylphenyl sulfide (28a) and



Compounds **28a,28b** were obtained from **5a** (0.53 g, 1.50 mmol), 2-*n*-propyl thiophenol (0.025 g, 1.65 mmol) and caesium carbonate (0.59 g, 1.8 mmol, 1.2 eq) in dimethylformamide (5 ml) following a modification of **General Procedure 1** in which the reaction was heated at 95°C for 3 hours. After purification by SCX column chromatography (eluent: ammonia/methanol 1/1 [v/v]) **28a,28b** was obtained as a dark yellow oil (0.56 g, 90%%); MW 417.62; $C_{27}H_{31}NOS$; ^1H NMR ($CDCl_3$): 7.23-7.12 (6H, m), 7.06-7.11 (5H, m), 6.97-6.99 (2H, m), 6.87-6.92 (1H, m), 4.13 (1H, d, 8 Hz), 3.86-3.94 (2H, m), 3.61 (1H, td, 11 Hz, 2 Hz), 3.44 (1H, d, 13 Hz), 3.23 (1H, d, 13 Hz), 2.46-2.59 (4H, m), 2.01-2.14 (2H, m), 1.34-1.52 (2H,

m), 0.83 (3H, t, 7 Hz); LCMS (2.5 minute method): *m/z* 418 $[M+H]^+$ @ R_t 1.55 min.

(2*S*)-2-{(*S*)-Phenyl[(2-propylphenyl)thio]methyl}morpholine (29)



Compound **29** (**Example 11**) was obtained from **28a,28b** (0.56 g, 1.35 mmol), solid supported Hünig's base (Argonaut, 3.56 mmol/g, 0.75 g, 2.7 mmol, 2 eq) and α-chloroethyl chloroformate (0.44 ml, 4.05 mmol, 3 eq) in anhydrous dichloromethane (5 ml) following **General Procedure 2** as a viscous yellow oil (0.41 g, 93%); MW 327.49; $C_{20}H_{25}NOS$; ^1H NMR ($CDCl_3$): 7.17 (1H, br, d, 7 Hz), 7.07-7.12 (5H, m), 6.96-7.00 (2H, m), 6.88-6.93 (1H, m), 4.07 (1H, d, 8 Hz), 3.93-3.98 (1H, m), 3.74-3.80 (1H, m), 3.60 (1H, td, 11 Hz, 3 Hz), 2.81 (1H, td, 12 Hz and 3 Hz), 2.72 (1H, br, d, 12 Hz), 2.48-2.62 (4H, m), 1.36-1.59 (3H, m), 0.83 (3H, t, 7 Hz); LCMS (2.5 minute method): *m/z* 328 $[M+H]^+$ @ R_t 1.40 min (single major peak).

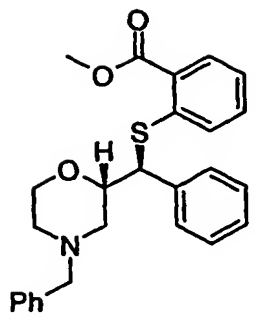
Example 12:

Methyl 2-{[(*S*)-(2*S*)-morpholin-2-yl(phenyl)methyl]thio}benzoate (31)

Methyl-2-({(*S*)-phenyl[(2*S*)-4-(phenylmethyl)morpholin-2-yl]methyl}thio)benzoate (30a)

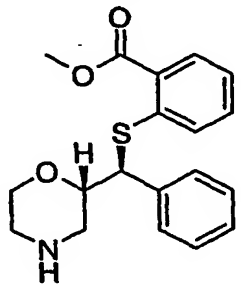
and

Methyl-2-({(*R*)-phenyl[(2*R*)-4-(phenylmethyl)morpholin-2-yl]methyl}thio)benzoate (30b)



Compounds **30a,30b** were obtained from **5a,5b** (0.5 g, 1.45 mmol), methyl thiosalicylate (0.49 g, 2.89 mmol) and potassium carbonate (0.21 g, 1.52 mmol) in dry tetrahydrofurane (5 ml) following modification of **General Procedure 1** in which the solvents were degassed and purged with nitrogen before the addition of methyl thiosalicylate. The reaction mixture was stirred at room temperature for 18 hours after which time the reaction mixture was poured onto water and extracted twice with diethyl ether. The organic layers were washed with water, dried and evaporated *in vacuo*. After purification by SCX column chromatography (eluent: ammonia/methanol 1/1 [v/v]) **30a,30b** was obtained as a colourless solid (0.18 g, 29%%); MW 433.57; $C_{26}H_{27}NO_3S$; ^1H NMR ($CDCl_3$): 8.65-8.85 (1H, m), 6.95-7.45 (13H, m), 4.45 (1H, d, 8 Hz), 3.85-4.05 (1H, m), 3.8 (3H, s), 3.65 (1H, dt, 1 Hz and 7 Hz), 3.55 (1H, d, 11 Hz), 3.25 (1H, d, 11 Hz), 2.5-2.6 (2H, m); 2.0-2.15 (2H, m); FIA: *m/z* 462 $[M+H]^+$.

Methyl 2-{[(*S*)-(2*S*)-morpholin-2-yl(phenyl)methyl]thio}benzoate (31)



Compound **31 (Example 12)** was obtained from **30a,30b** (0.2 g, 0.46 mmol), solid supported Hünig's base (Argonaut, 3.56 mmol/g, 0.08 g, 2.77 mmol, 6 eq) and α-chloroethyl chloroformate (0.5 ml, 4.62 mmol, 10 eq) in anhydrous dichloromethane (5 ml) following **General Procedure 2** as a white solid (0.16 g,

91%) from which **31** was obtained after separation using chiral HPLC on chiral OJ semi-preparative column. Chiral LC (OJ): 12.32 min. LC purity = 100% (UV_{254nm}); MW 343.45. **31** was converted into its hydrochloride salt following **General Procedure 3**; ^1H NMR (d_6-DMSO): 9.30-9.5 (1H, m), 7.75-7.80 (1H, m), 7.1-7.55 (8H, m), 4.82 (1H, d, 8 Hz), 3.95-4.15 (2H, m), 3.65.3.9 (3H, m), 3.55 (3H, s), 2.80-3.25 (2H, m).

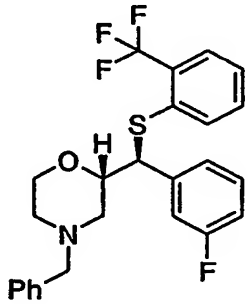
Example 13:

(2*S*)-2-((*S*)-(3-Fluorophenyl){[2-(trifluoromethyl)phenyl]thio}methyl) morpholine (33)

(2*S*)-2-((*S*)-(3-Fluorophenyl){[2-(trifluoromethyl)phenyl]thio}methyl)-4-(phenylmethyl)morpholine (32a)

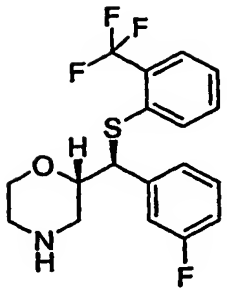
and

(2*R*)-2-((*R*)-(3-Fluorophenyl){[2-(trifluoromethyl)phenyl]thio}methyl)-4-(phenylmethyl)morpholine (32b)



Compounds **32a,32b** were obtained as outlined in **Scheme 5** from **38a,38b** (0.33 g, 0.91 mmol) following **General Procedure 4** as a white solid after column chromatography (0.28 g, 67%); MW 461.53; $C_{25}H_{23}F_4NOS$; ^1H NMR ($CDCl_3$) 6.75-7.65 (1H, m), 6.85-7.33 (12H, m), 4.45 (2H, d, 8 Hz), 3.6-3.75 (2H, m), 3.45 (1H, d 12 Hz), 3.3 (1H, d 12 Hz), 2.45-2.7 (2H, br, m),), 2.1-2.3 (2H, br, m); FIA: *m/z* 462 $[M+H]^+$.

(2*S*)-2-((*S*)-(3-Fluorophenyl){[2-(trifluoromethyl)phenyl]thio}methyl)morpholine (33)



Compound **33** (**Example 13**) was obtained from **32a,32b** (0.28 g, 0.615 mmol), solid supported Hünig's base (Argonaut, 3.56 mmol/g, 0.19 g, 0.68 mmol, 1.1 eq) and α-chloroethyl chloroformate (0.07 ml, 0.68 mmol, 1.1 eq) in anhydrous dichloromethane (5 ml) following **General Procedure 2** as a colourless oil (0.22 g, 95%) from which **33** was obtained after chiral chromatography on a Chiralcel OJ semi-preparative column. Chiral LC (OJ): 13.33 min. LC purity = 98.37% (UV_{254nm}); MW 371.4; $C_{18}H_{17}F_4NOS$. LCMS (12 minute method): m/z 372 [M+H]+ @ Rt 5.2 min. **33** was converted into its hydrochloride salt following **General Procedure 3**; MW 407.86; $C_{18}H_{17}F_4NOS.HCl$; ^1H NMR ($CDCl_3$) 9.8-10.2 (1H, br), 7.4-7.6 (1H, m), (6.85-7.45 (8H, m), 4.05-4.45 (4H, br, m), 2.90-3.41 (4H, br, m).

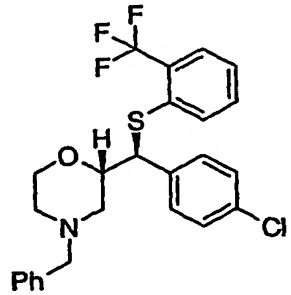
Example 14:

(2*S*)-2-((*S*)-(4-Chlorophenyl){[2-(trifluoromethyl)phenyl]thio}methyl) morpholine (35)

(2*S*)-2-((*S*)-(4-Chlorophenyl){[2-(trifluoromethyl)phenyl]thio}methyl)-4-(phenylmethyl)morpholine (34a)

and

(2*R*)-2-((*R*)-(4-Chlorophenyl){[2-(trifluoromethyl)phenyl]thio}methyl)-4-(phenylmethyl)morpholine (34b)



Compounds **34a,34b** were obtained as outlined in **Scheme 5** from **39a,39b** (0.4 g, 1.06 mmol, 1.1 eq), cesium carbonate (0.33 g, 1.0 mmol, 1.1 eq), and 2-trifluoromethyl benzene thiol (0.19 g, 1.06 mmol, 1.1 eq) following a modification of **General Procedure 1** in which the reaction was stirred at room temperature for 1.5 hours as a white solid after column chromatography (eluent: gradient hexane/ethyl acetate 10/90 to 25/75[v/v]) (0.409g, 80%); MW 477.98; $C_{25}H_{23}F_3ClNOS$; ^1H NMR ($CDCl_3$) 7.1-7.65 (13H, m), 4.45 (1H, d, 8 Hz), 3.85-4.0 (2H, m), 3.55 (1H, m), 3.3 (1H, d 12 Hz), 3.3 (1H, d 12 Hz), 2.45-2.65 (2H, br),), 2.1-2.3 (2H, br, m); FIA: *m/z* 478 $[M+H]^+$.

(2*S*)-2-((*S*)-(4-Chlorophenyl){[2-(trifluoromethyl)phenyl]thio}methyl)morpholine (35)

Compound **35 (Example 14)** was obtained from **34a,34b** (0.41 g, 0.86 mmol), solid supported Hünig's base (Argonaut, 3.56 mmol/g, 0.27 g, 0.94 mmol, 1.1 eq) and α-chloroethyl chloroformate (0.10 ml, 0.94 mmol, 1.1 eq) in anhydrous dichloromethane (5 ml) following **General Procedure 2** as a colourless oil (0.28 g, 84% yield) from which **35** was obtained after separation using chiral HPLC on a ChiralPak-AD OJ semi-preparative column; MW 387.85; $C_{18}H_{17}ClF_3NOS$; LCMS (12 minute method): m/z 372 [M+H]+ @ Rt 5.2 min. **35** was converted into its hydrochloride salt following **General Procedure 3**; MW 423.96; $C_{18}H_{17}ClF_3NOS.HCl$; ^1H NMR ($CDCl_3$): 9.8-10.2 (1H, br), 7.4-7.6 (1H, m), 7.07-7.35 (7H, m), 3.8-4.45 (4H, br, m), 2.85-3.45 (4H, br, m).

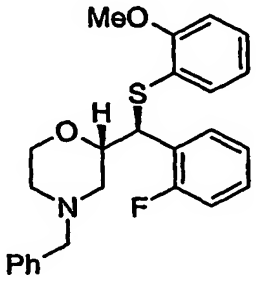
Example 15:

(2*S*)-2-((*S*)-(2-Fluorophenyl){[2-(methyloxy)phenyl]thio}methyl)morpholine (37)

(2*S*)-2-((*S*)-(2-Fluorophenyl){[2-(methyloxy)phenyl]thio}methyl)-4-(phenylmethyl)morpholine (36a)

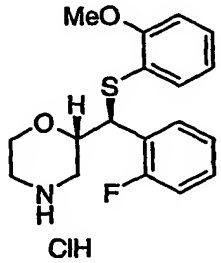
and

(2*R*)-2-((*R*)-(2-Fluorophenyl){[2-(methyloxy)phenyl]thio}methyl)-4-(phenylmethyl)morpholine (36b)



Compounds **36a,36b** were obtained from **7a,7b** (0.45 g, 1.17 mmol), cesium carbonate (0.42 g, 1.29 mmol, 1.1 eq), and 2-methoxy-thiophenol (0.82 g, 5.87 mmol) following a modification of **General Procedure 1** in which the reaction mixture was heated to 95°C for 2 hours and then stirred at room temperature for 18 hours. After purification by flash column chromatography (eluent: heptane/ethyl acetate 80/20 [v/v]) **18,18b** was obtained as a colourless oil (0.36 g, 72%%); MW 423.55; $C_{25}H_{26}FNOS$; ^1H NMR ($CDCl_3$): 6.65-7.5 (13H, m), 4.9 (1H, d, 7 Hz), 3.9-4.05 (2H, m), 3.8 (3H, s), 3.6 (1H, dt, 8 Hz and 1 Hz), 3.45 (1H, d, 13 Hz), 3.15 (1H, d, 13 Hz), 2.60 (2H, t, 8 Hz), 2.05-2.2 (2H, m); FIA: *m/z* 424 $[M+H]^+$.

(2*S*)-2-((*S*)-(2-Fluorophenyl){[2-(methyloxy)phenyl]thio}methyl)morpholine (37)



Compound **37** (**Example 15**) was obtained from **36a,36b** (0.43 g, 1.02 mmol), solid supported Hünig's base (Argonaut, 3.56 mmol/g, 0.37 g, 1.12 mmol, 1.1 eq) and α-chloroethyl chloroformate (1.08 ml, 10.12 mmol, 10 eq) in anhydrous dichloromethane (5 ml) following **General Procedure 2** as a colourless oil (0.34 g,

99%) after separation by chiral HPLC on a ChiralPak-AD semi-preparative column. Chiral LC: 12.86 min. LC purity = 99.1 (UV_{254nm}); MW 369.89; $C_{18}H_{20}FNOS$; FIA: *m/z* 334 $[M+H]^+$. **37** was converted into its hydrochloride salt following **General Procedure 3**; MW 333.43; $C_{18}H_{20}FNOS$; ^1H NMR ($CDCl_3$): 7.2-7.3 (1H, m), 6.85-7.2 (8H, m), 4.85 (1H, d, 8 Hz), 3.95-4.15 (2H, m), 3.85.3.9 (3H, m), 3.7 (1H, dt, 1 Hz and 7 Hz), 2.6-3.0 (4H, m).

The compounds of the present invention may be used as medicaments in human or veterinary medicine. The compounds may be administered by various routes, for example, by oral or rectal routes, topically or parenterally, for example by injection, and are usually employed in the form of a pharmaceutical composition.

Such compositions may be prepared by methods well known in the pharmaceutical art and normally comprise at least one active compound in association with a pharmaceutically acceptable diluent or carrier. In making the compositions of the present invention, the active ingredient will usually be mixed with a carrier or diluted by a carrier, and/or enclosed within a carrier which may, for example, be in the form of a capsule, sachet, paper or other container. Where the carrier serves as a diluent, it may be solid, semi-solid, or liquid material which acts as a vehicle, excipient or medium for the active ingredient. Thus, the composition may be in the form of tablets, lozenges, sachets, cachets, elixirs, suspensions, solutions, syrups, aerosol (as a solid or in a liquid medium), ointments containing, for example, up to 10% by weight of the active compound, soft and hard gelatin capsules, suppositories, injection solutions and suspensions and sterile packaged powders.

Some examples of suitable carriers are lactose, dextrose, vegetable oils, benzyl alcohols, alkylene glycols, polyethylene glycols, glycerol triacetate, gelatin, carbohydrates such as starch and petroleum jelly, sucrose sorbitol, mannitol, starches, gum acacia,calcium phosphate, alginates, tragacanth, gelatin, syrup, methyl cellulose, methyl- and propyl- hydrobenzoate, talc, magnesium stearate and mineral oil. The compounds of formula (I) can also be lyophilized and the lyophilizates obtained used, for example, for the production of injection preparations. The preparations indicated can be sterilized and/or can contain auxiliaries such as

auxiliaries such as lubricants, preservatives, stabilizers and/or wetting agents, emulsifiers, salts for affecting the osmotic pressure, buffer substances, colourants, flavourings and/or one or more further active compounds, e.g. one or more vitamins. Compositions of the invention may be formulated so as to provide, quick, sustained or delayed release of the active ingredient after administration to the patient by employing procedures well known in the art.

The compositions are preferably formulated in a unit dosage form, each dosage containing from about 5 to about 500 mg, more usually about 25 to about 300 mg, of the active ingredient. The term "unit dosage form" refers to physically discrete units suitable as unitary doses for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical carrier.

The pharmacological profile of the present compounds may be demonstrated as follows.

Scintillation proximity assays for determining the affinity of test ligands at the norepinephrine transporter.

The compounds of the invention are norepinephrine reuptake inhibitors, and possess excellent activity in, for example, a scintillation proximity assay (e.g. J. Gobel, D.L. Saussy and A. Goetz, J. Pharmacol. Toxicolo. (1999), 42, 237-244). Thus ^{3}H-nisoxetine binding to norepinephrine re-uptake sites in a cell line transfected with human norepinephrine transporter binding has been used to determine the affinity of ligands at the norepinephrine transporter.

In Vitro Determination of the Interaction of Compounds with CYP2D6 in Human Hepatic Microsomes

Principle:

The interaction of compounds with CYP2D6 was evaluated by the measurement of the inhibition of the bufurolol 1'-hydroxylase activity by the compounds.

Assay description:

Bufuralol 1-hydroxylase activity is determined by using 0.5 mg/ml human liver microsomal protein (human biologics), 10 μmol/L bufuralol, in 0.1 M sodium phosphate buffer pH 7.4, incubated for 5 min at 37°C in the presence of 2 mM βNADPH, with 0, 5 or 25 μM of the test compound (inhibitor). The compound was dissolved in acetonitrile, such that the final concentration of acetonitrile in the incubation was 0.5%. The total reaction volume was 100 μl. The reaction was terminated by addition of 75 μl of methanol followed by centrifugation. 40 μl of the supernatant was analysed by HPLC.

Analysis conditions:

A Beckman Ultrasphere C_{18} column (5 μm, 250 x 4.6 mm) was used, with a 13 minute gradient from 100% of solvent A (0.02 M potassium dihydrogen phosphate buffer pH 3/methanol (65/35)) to 100 % of solvent B (0.02 M potassium dihydrogen phosphate buffer pH 3/methanol (20/80)), according to the following gradient. The run time was 20 minutes. Formation of 1'-hydroxybufuralol was detected by fluorimetric detection with extinction at λ 252 nm and emission at λ 302 nm.

Time (min)	Solvent A (%)	Solvent B (%)
0	100	0
8	0	100
12	0	100
13	100	0

Calculation of the results:

The percent of inhibition is calculated as follows:

$$100 - \frac{100 \times \text{1'-hydroxybufuralol area formed with inhibitor}}{\text{1'-hydroxybufuralol area formed without inhibitor}}$$

The IC_{50} is calculated from the percent inhibition as follows (assuming competitive inhibition): $\frac{\text{Compound Concentration} \times (100 - \text{Percent of inhibition})}{\text{Percent of inhibition}}$

The IC_{50} estimation is assumed valid if inhibition is between 20% and 80% (Moody 1999).

X-RAY CRYSTALLOGRAPHIC DATA FOR THE COMPOUND OF EXAMPLE 1

Table 1. Crystal data and structure refinement for 2003xf.

Identification code	2003xf	
Empirical formula	C18 H19 Cl F3 N O S	
Formula weight	389.85	
Temperature	107(2) K	
Wavelength	0.71073 A	
Crystal system, space group	Monoclinic, P2(1)	
Unit cell dimensions	a = 9.984(2) A	alpha = 90 deg.
	b = 5.6484(13) A	beta = 100.867(4) deg.
	c = 15.931(4) A	gamma = 90 deg.
Volume	882.4(4) A^3	
Z, Calculated density	2, 1.467 Mg/m^3	
Absorption coefficient	0.371 mm^-1	
F(000)	404	
Crystal size	.06 x .08 x .18 mm	
Theta range for data collection	1.30 to 28.20 deg.	
Limiting indices	11<=h<=13, -7<=k<=7, -20<=l<=19	
Reflections collected / unique	5986 / 3378 [R(int) = 0.0661]	
Completeness to theta = 28.20	92.9 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3378 / 1 / 234	
Goodness-of-fit on F^2	0.846	
Final R indices [I>2sigma(I)]	R1 = 0.0488, wR2 = 0.0908	
R indices (all data)	R1 = 0.1227, wR2 = 0.1101	
Absolute structure parameter	0.11(10)	
Largest diff. peak and hole	0.548 and -0.444 e.A^-3	

X-RAY CRYSTALLOGRAPHIC DATA FOR THE COMPOUND OF EXAMPLE 1

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for 2003xf.

U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)	
	S(8)	8641(1)	5291(2)	2641(1)	35(1)
	O(1)	10279(3)	2645(5)	4200(2)	24(1)
	C(7)	9992(5)	3088(8)	2678(3)	25(1)
	F(3)	5136(4)	4842(7)	443(2)	65(1)
	N(4)	13055(4)	1352(9)	4386(3)	21(1)
	C(5)	12147(4)	1431(8)	3536(3)	22(1)
	F(2)	7264(4)	4253(5)	644(2)	51(1)
	C(20)	10490(5)	1794(8)	1263(3)	31(1)
	F(1)	6497(4)	7227(5)	1228(2)	48(1)
	C(15)	10669(5)	3416(8)	1925(3)	24(1)
	C(6)	11008(5)	3187(8)	3525(3)	24(1)
	C(16)	11472(5)	5394(10)	1846(3)	32(1)
	C(10)	6184(5)	3389(9)	1805(3)	26(1)
	C(13)	5978(5)	382(11)	3117(4)	40(1)
	C(9)	7190(5)	3438(9)	2506(3)	30(1)
	C(3)	12283(5)	976(8)	5085(3)	27(1)
	C(12)	4992(5)	364(10)	2423(3)	31(1)
	C(2)	11168(5)	2787(9)	5010(3)	28(1)
	C(21)	6253(6)	4934(11)	1033(4)	41(2)
	C(18)	11846(5)	4080(10)	494(3)	33(1)
	C(17)	12048(5)	5721(9)	1131(4)	36(1)
	C(19)	11078(5)	2138(9)	552(4)	35(1)
	C(11)	5062(5)	1943(9)	1738(4)	42(2)
	C(14)	7065(6)	1852(10)	3160(4)	43(2)
	Cl(1)	4131(1)	6360(2)	4214(1)	30(1)

X-RAY CRYSTALLOGRAPHIC DATA FOR THE COMPOUND OF EXAMPLE 1

Table 3. Bond lengths [A] and angles [deg] for 2003xf.

S(8)-C(9)	1.767(5)
S(8)-C(7)	1.828(5)
O(1)-C(2)	1.424(5)
O(1)-C(6)	1.440(5)
C(7)-C(15)	1.495(6)
C(7)-C(6)	1.528(6)
F(3)-C(21)	1.318(6)
N(4)-C(5)	1.481(5)
N(4)-C(3)	1.484(6)
C(5)-C(6)	1.507(6)
F(2)-C(21)	1.337(6)
C(20)-C(19)	1.385(7)
C(20)-C(15)	1.383(6)
F(1)-C(21)	1.343(6)
C(15)-C(16)	1.395(6)
C(16)-C(17)	1.382(7)
C(10)-C(9)	1.354(6)
C(10)-C(11)	1.374(7)
C(10)-C(21)	1.520(8)
C(13)-C(12)	1.334(6)
C(13)-C(14)	1.358(7)
C(9)-C(14)	1.397(7)
C(3)-C(2)	1.500(6)
C(12)-C(11)	1.421(7)
C(18)-C(19)	1.351(7)
C(18)-C(17)	1.360(7)
C(9)-S(8)-C(7)	100.6(2)
C(2)-O(1)-C(6)	110.4(4)
C(15)-C(7)-C(6)	112.3(4)
C(15)-C(7)-S(8)	109.4(3)
C(6)-C(7)-S(8)	111.5(3)
C(5)-N(4)-C(3)	112.0(4)
N(4)-C(5)-C(6)	11.2(4)

	C(19)-C(20)-C(15)	121.2(5)
	C(20)-C(15)-C(16)	117.1(5)
	C(20)-C(15)-C(7)	121.1(5)
	C(16)-C(15)-C(7)	121.8(5)
5	O(1)-C(6)-C(5)	109.7(4)
	O(1)-C(6)-C(7)	107.9(4)
	C(5)-C(6)-C(7)	111.1(4)
	C(17)-C(16)-C(15)	121.2(5)
	C(9)-C(10)-C(11)	122.9(5)
10	C(9)-C(10)-C(21)	121.0(5)
	C(11)-C(10)-C(21)	116.0(5)
	C(12)-C(13)-C(14)	120.3(6)
	C(10)-C(9)-C(14)	116.4(5)
	C(10)-C(9)-S(8)	125.2(4)
15	C(14)-C(9)-S(8)	118.4(4)
	N(4)-C(3)-C(2)	109.0(4)
	C(13)-C(12)-C(11)	119.7(5)
	O(1)-C(2)-C(3)	111.1(4)
	F(3)-C(21)-F(1)	107.1(5)
20	F(3)-C(21)-F(2)	105.6(5)
	F(1)-C(21)-F(2)	105.4(5)
	F(3)-C(21)-C(10)	113.2(5)
	F(1)-C(21)-C(10)	113.6(5)
	F(2)-C(21)-C(10)	111.4(5)
25	C(19)-C(18)-C(17)	120.6(5)
	C(18)-C(17)-C(16)	119.8(5)
	C(18)-C(19)-C(20)	120.2(5)
	C(10)-C(11)-C(12)	118.1(5)
	C(13)-C(14)-C(9)	122.5(5)

30

Symmetry transformations used to generate equivalent atoms:

X-RAY CRYSTALLOGRAPHIC DATA FOR THE COMPOUND OF EXAMPLE 1

Table 4. Anisotropic displacement parameters (A^2 x 10^3) for 2003xf.
The anisotropic displacement factor exponent takes the form: -2 pi^2 [h^2 a*^2 U11 + ... + 2 h k a* b* U12]

	U11	U22	U33	U23	U13	U12
S(8)	24(1)	24(1)	53(1)	-1(1)	-1(1)	4(1)
O(1)	24(2)	23(2)	24(2)	3(2)	0(2)	-2(2)
C(7)	20(3)	23(2)	27(3)	-3(2)	-8(3)	0(2)
F(3)	55(2)	88(3)	42(2)	15(2)	-16(2)	-13(2)
N(4)	19(2)	14(2)	31(3)	3(2)	3(2)	-3(3)
C(5)	22(3)	16(2)	26(3)	-4(2)	2(2)	2(3)
F(2)	69(3)	53(2)	39(2)	5(2)	29(2)	3(2)
C(20)	29(3)	28(3)	31(3)	-12(3)	-5(3)	-1(2)
F(1)	61(2)	35(2)	46(2)	5(2)	5(2)	5(2)
C(15)	20(3)	22(3)	27(3)	2(3)	-3(2)	5(2)
C(6)	23(3)	17(2)	33(3)	-1(2)	11(3)	1(2)
C(16)	40(3)	22(2)	31(3)	-3(3)	1(3)	-7(3)
C(10)	20(3)	30(3)	27(3)	2(3)	8(3)	4(3)
C(13)	33(3)	45(3)	42(4)	3(3)	7(3)	0(3)
C(9)	20(3)	38(3)	31(4)	-8(3)	2(3)	7(3)
C(3)	22(3)	28(3)	32(3)	10(2)	5(2)	0(2)
C(12)	22(3)	29(2)	41(4)	-1(3)	8(3)	-7(3)
C(2)	28(3)	34(3)	22(3)	-2(3)	3(3)	4(2)
C(21)	27(4)	50(4)	43(4)	-16(3)	-1(3)	10(3)
C(18)	24(3)	44(3)	30(4)	-1(3)	3(3)	11(3)
C(17)	42(4)	26(3)	40(4)	0(3)	9(3)	-6(2)
C(19)	33(3)	38(3)	33(4)	-9(3)	2(3)	6(3)
C(11)	20(3)	49(4)	52(4)	-18(3)	-3(3)	8(3)
C(14)	35(4)	72(5)	22(3)	16(3)	-1(3)	-4(3)
Cl(1)	24(1)	16(1)	46(1)	1(1)	-1(1)	-1(1)

X-RAY CRYSTALLOGRAPHIC DATA FOR THE COMPOUND OF EXAMPLE 1

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (A^2 x 10^3) for 2003xf.

	x	y	z	U(eq)
H(7A)	9558	1486	2630	30
H(5A)	11757	-162	3392	26
H(5B)	12685	1877	3099	26
H(20A)	9954	420	1297	37
H(6A)	11398	4819	3611	29
H(16A)	11626	6536	2292	38
H(13A)	5919	-637	3583	48
H(3A)	12902	1128	5645	33
H(3B)	11886	-636	5043	33
H(12A)	4246	-700	2387	37
H(2A)	10639	2529	5468	34
H(2B)	11575	4389	5085	34
H(18A)	12248	4302	5	40
H(17A)	12584	7087	1084	43
H(19A)	10941	1005	103	42
H(11A)	4354	1998	1248	50
H(14A)	7767	1799	3653	52
H(4B)	13680(60)	2600(100)	4430(30)	53(19)
H(4A)	13580(50)	230(90)	4400(30)	29(17)

X-RAY CRYSTALLOGRAPHIC DATA FOR THE COMPOUND OF EXAMPLE 1

Table 6. Torsion angles [deg] for 2003xf.

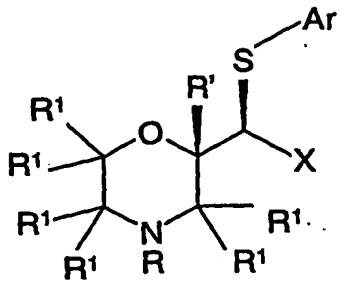
C(9)-S(8)-C(7)-C(15)	115.5(4)
C(9)-S(8)-C(7)-C(6)	-119.7(4)
C(3)-N(4)-C(5)-C(6)	52.2(6)
C(19)-C(20)-C(15)-C(16)	-0.4(7)
C(19)-C(20)-C(15)-C(7)	177.8(4)
C(6)-C(7)-C(15)-C(20)	126.4(5)
S(8)-C(7)-C(15)-C(20)	-109.2(4)
C(6)-C(7)-C(15)-C(16)	-55.5(6)
S(8)-C(7)-C(15)-C(16)	68.9(5)
C(2)-O(1)-C(6)-C(5)	60.7(5)
C(2)-O(1)-C(6)-C(7)	-178.1(4)
N(4)-C(5)-C(6)-O(1)	-55.1(5)
N(4)-C(5)-C(6)-C(7)	-174.3(4)
C(15)-C(7)-C(6)-O(1)	-175.0(4)
S(8)-C(7)-C(6)-O(1)	61.9(4)
C(15)-C(7)-C(6)-C(5)	-54.7(5)
S(8)-C(7)-C(6)-C(5)	-177.8(3)
C(20)-C(15)-C(16)-C(17)	0.7(7)
C(7)-C(15)-C(16)-C(17)	-177.4(5)
C(11)-C(10)-C(9)-C(14)	2.6(8)
C(21)-C(10)-C(9)-C(14)	-176.4(5)
C(11)-C(10)-C(9)-S(8)	-178.8(4)
C(21)-C(10)-C(9)-S(8)	2.2(7)
C(7)-S(8)-C(9)-C(10)	-114.6(5)
C(7)-S(8)-C(9)-C(14)	64.0(5)
C(5)-N(4)-C(3)-C(2)	-52.6(6)
C(14)-C(13)-C(12)-C(11)	-1.9(8)
C(6)-O(1)-C(2)-C(3)	-63.3(5)
N(4)-C(3)-C(2)-O(1)	58.2(5)
C(9)-C(10)-C(21)-F(3)	-173.8(5)
C(11)-C(10)-C(21)-F(3)	7.1(7)
C(9)-C(10)-C(21)-F(1)	-51.3(7)
C(11)-C(10)-C(21)-F(1)	129.6(5)

C(9)-C(10)-C(21)-F(2)	67.4(7)
C(11)-C(10)-C(21)-F(2)	-111.6(5)
C(19)-C(18)-C(17)-C(16)	0.5(8)
C(15)-C(16)-C(17)-C(18)	-0.7(8)
C(17)-C(18)-C(19)-C(20)	-0.2(8)
C(15)-C(20)-C(19)-C(18)	0.1(8)
C(9)-C(10)-C(11)-C(12)	-2.7(8)
C(21)-C(10)-C(11)-C(12)	176.3(5)
C(13)-C(12)-C(11)-C(10)	2.3(8)
C(12)-C(13)-C(14)-C(9)	1.9(8)
C(10)-C(9)-C(14)-C(13)	-2.1(8)
S(8)-C(9)-C(14)-C(13)	179.2(4)

Symmetry transformations used to generate equivalent atoms

CLAIMS

1. A compound of formula (I)



wherein:

R is H;

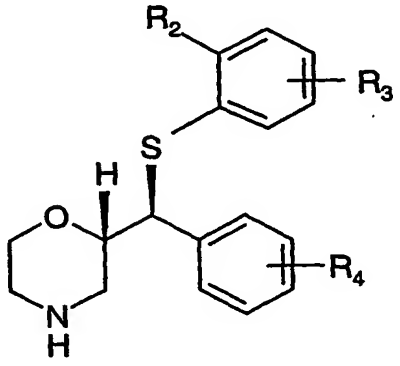
Ar is a phenyl group;

X is a phenyl group;

R' is H or C_1-C_4 alkyl;

each R^1 is independently H or C_1-C_4 alkyl; and pharmaceutically acceptable salts thereof.

2. A compound as claimed in claim 1, represented by the formula (II);



(II)

wherein

R_2 and R_3 are each independently selected from H, C_1-C_4 alkyl, O(C_1-C_4 alkyl), S(C_1-C_4 alkyl), halo and phenyl; and

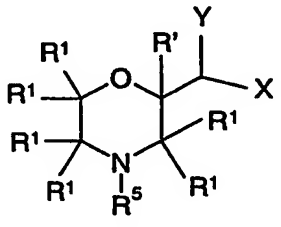
R_4 is selected from H and C_1-C_4 alkyl; and pharmaceutically acceptable salts thereof.

3. A compound as claimed in claim 2, wherein R_2 is selected from C_1-C_4 alkyl, O(C_1-C_4 alkyl), F and Ph.

4. A compound as claimed in any one of claims 2 and 3, wherein R_3 is hydrogen.

5. A compound as claimed in any one of claims 2, 3 and 4, wherein R_4 is hydrogen.

6. A method of preparing a compound as claimed in any one of the preceding claims, comprising reacting a compound of the formula II:



II

where R5 is a protecting group, e.g. benzyl, X R' and R^1 are as in formula I in claim 1 above and Y is a leaving group, with an aryl thiol.

7. A compound as claimed in any one of claims 1-5, for use as a pharmaceutical.

8. A compound as claimed in any one of claims 1-5, for use as a selective inhibitor of the reuptake of norpinephrine.

9. The use of a compound as claimed in any one of claims 1-5, for treating a disorder associated with norepinephrine dysfunction in mammals.

10. The use of a compound as claimed in any one of claims 1-5, for the manufacture of a medicament for treating a disorder associated with norepinephrine dysfunction in mammals.

11. A method for selectively inhibiting the reuptake of norepinephrine in mammals, comprising administering to a patient in need thereof an effective amount of a compound as claimed in any one of claims 1-5, or a pharmaceutically acceptable salt thereof.

12. A method for treating disorders associated with norepinephrine dysfunction in mammals, comprising administering to a patient in need thereof an effective amount of a compound as claimed in any one of claims 1-5, or a pharmaceutically acceptable salt thereof.

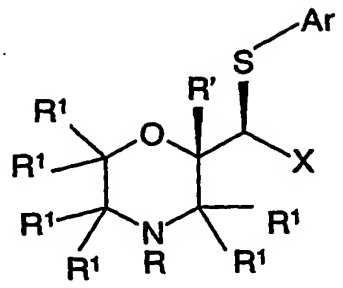
13. A method or use as claimed in any one of claims 9, 10 and 12, wherein the disorder is selected from nervous system conditions selected from the group consisting of an addictive disorder and withdrawal syndrome, an adjustment disorder, an age-associated learning and mental disorder, anorexia nervosa, apathy, an attention-deficit disorder (ADD) due to general medical conditions, attention-deficit hyperactivity disorder (ADHD), bipolar disorder, bulimia nervosa, chronic fatigue syndrome, chronic or acute stress, conduct disorder, cyclothymic disorder, depression, dysthymic disorder, fibromyalgia and other somatoform disorders, generalized anxiety disorder, incontinence, an inhalation disorder, an intoxication disorder, mania, migraine headaches, obesity, obsessive compulsive disorders and related spectrum disorders, oppositional defiant disorder, panic disorder, peripheral neuropathy, post-traumatic stress disorder, premenstrual dysphoric disorder, a psychotic disorder, seasonal affective disorder, a sleep disorder, social phobia, a specific developmental disorder, selective serotonin reuptake inhibition (SSRI) "poop out" syndrome, TIC disorders, cognitive disorders including mild cognitive impairment (MCI), dementia of the Alzheimers type (DAT), vascular dementia and

cognitive impairment associated with schizophrenia (CIAS), hypotensive states including orthostatic hypotension, and pain including chronic pain, neuropathic pain and antinociceptive pain.

14. A method or use as claimed in any one of claims 9, 10 and 12, wherein the disorder is attention deficit hyperactivity disorder, ADHD.

ABSTRACT

A compound of formula (I)



wherein:

R is H;

Ar is a phenyl group;

X is a phenyl group;

R' is H or C_1-C_4 alkyl;

each R^1 is independently H or C_1-C_4 alkyl; and pharmaceutically acceptable salts thereof.